

“Malaria: Mosquito Immunity and Transmission of the World's Major Killer”

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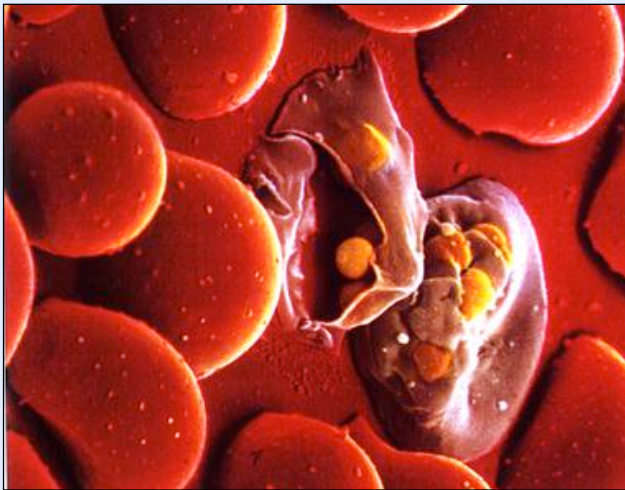
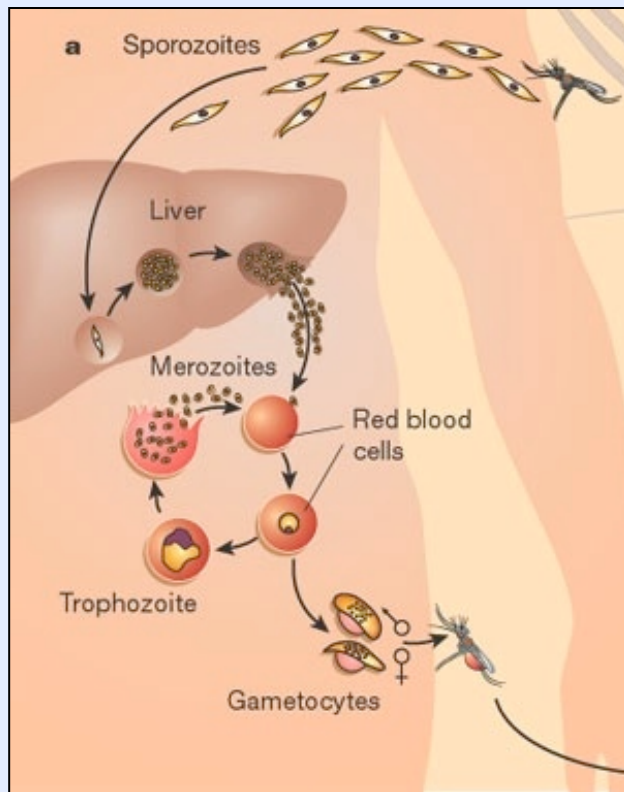


Malaria

Malaria is a public health problem affecting 40% of the world's population.

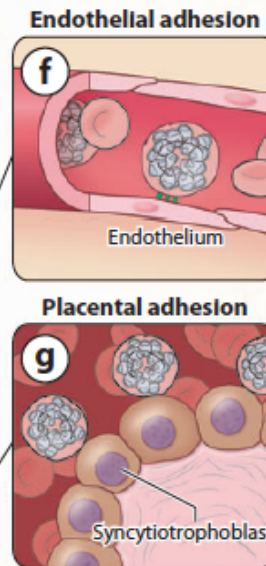
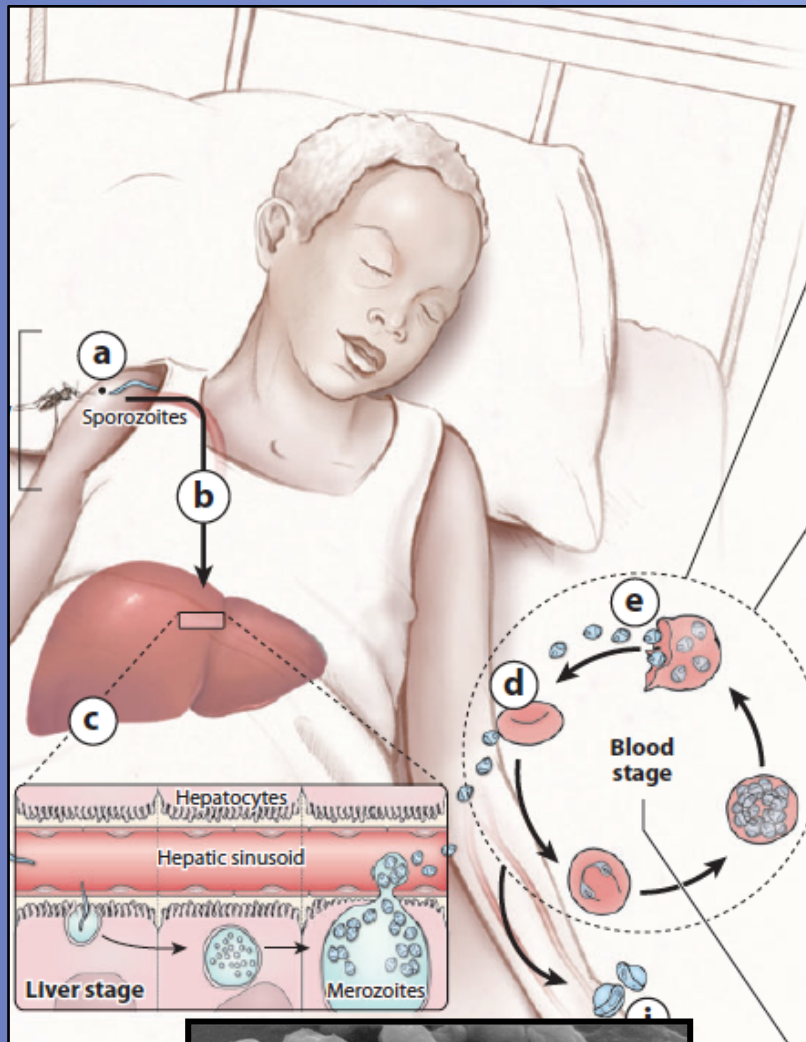
More than 90% of all cases are in sub-Saharan Africa.

Worldwide prevalence of the disease is estimated to be in order of 220 million cases and 660,000 deaths per year (WHO 2012).

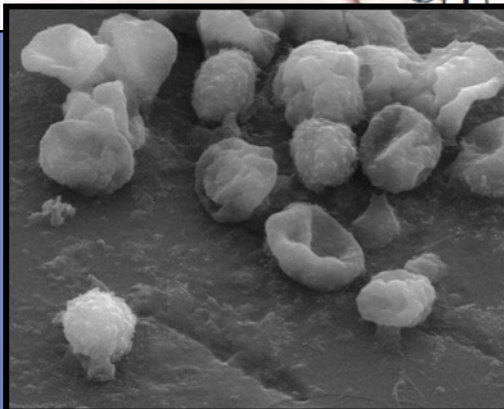


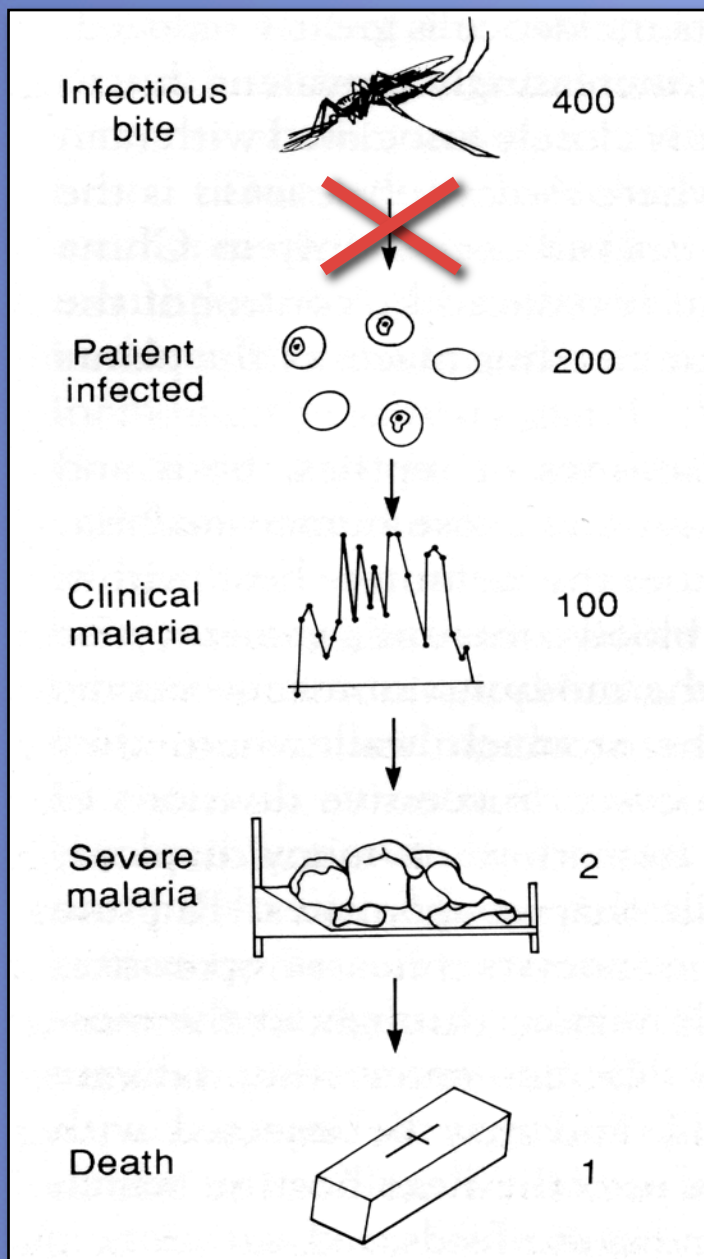
Malaria

- Malaria is caused by a parasite called *Plasmodium*, which is transmitted via the bites of infected mosquitoes.
- In the human body, the parasites multiply in the liver, and then infect red blood cells.



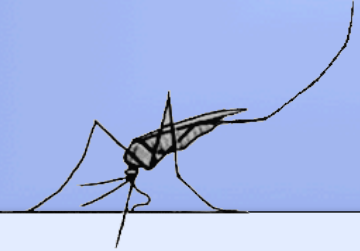
- The vast majority of deaths occur among young children in Africa.
- A child dies of malaria every 45 seconds.
- Each year an estimated 10,000 women and 200,000 of their infants die as a result of malaria infection during pregnancy.





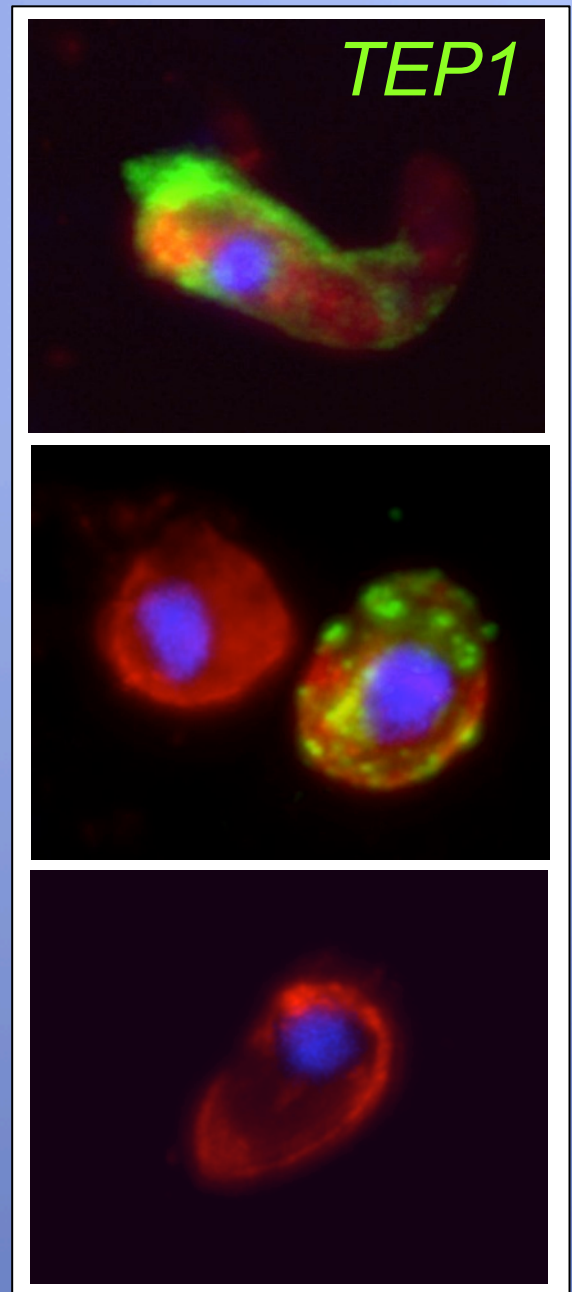
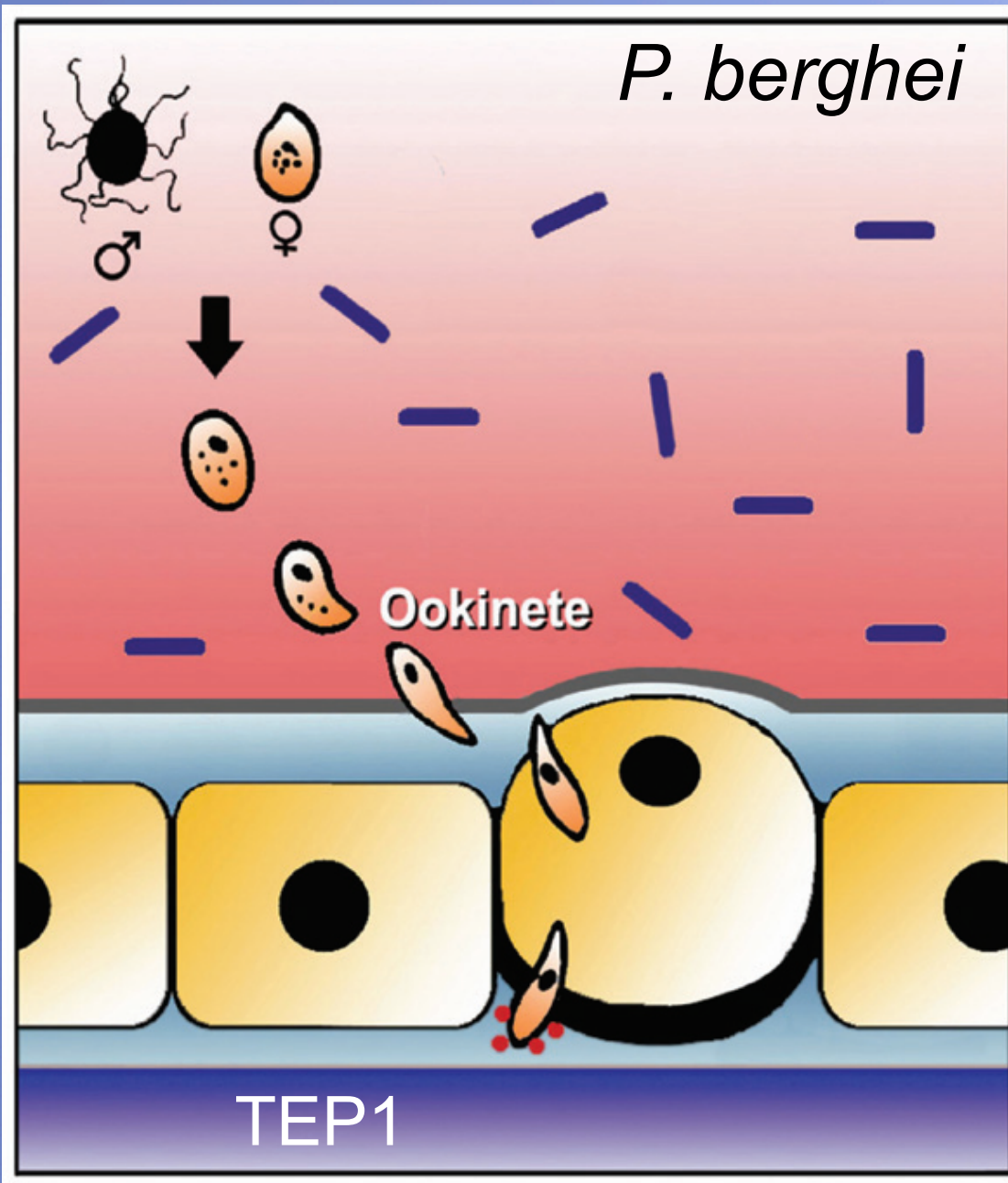
Anopheles gambiae is the major vector of malaria in Africa.





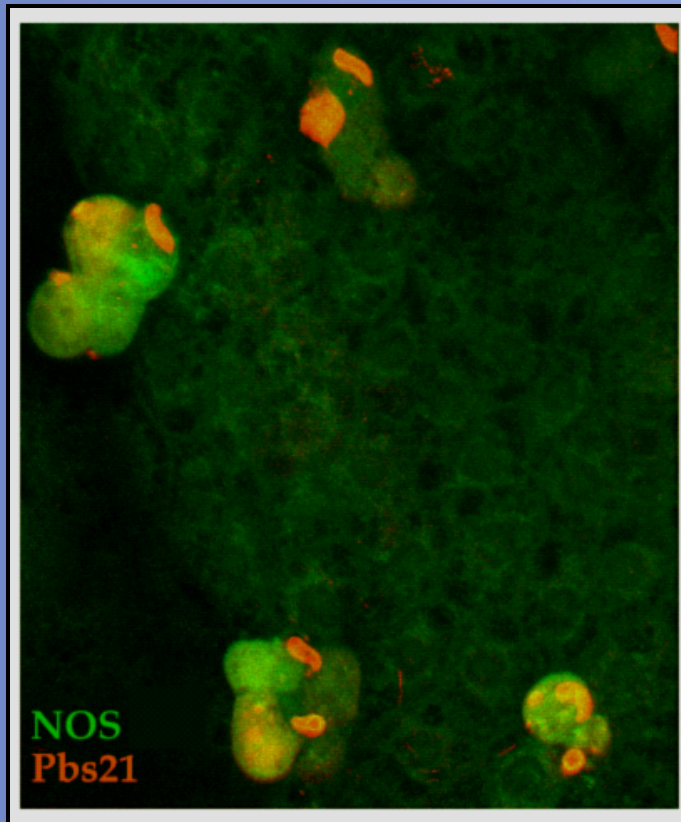
Outline

1. Midgut Epithelial Immunity and Complement Activation.
2. Participation of the JNK pathway in mosquito antiplasmodial immunity.
3. *Plasmodium falciparum* evasion of the mosquito immune system.

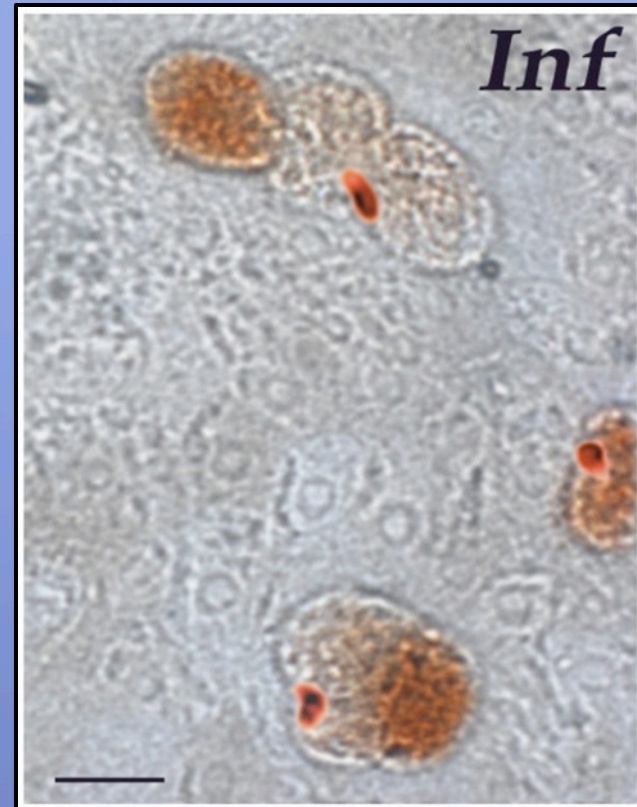


Hypothesis

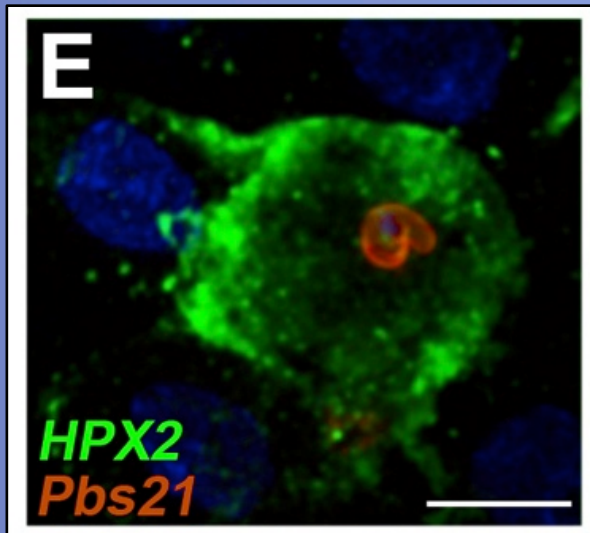
The nitration response is a two step reaction and the rate of these reactions determines the fate of the parasite.



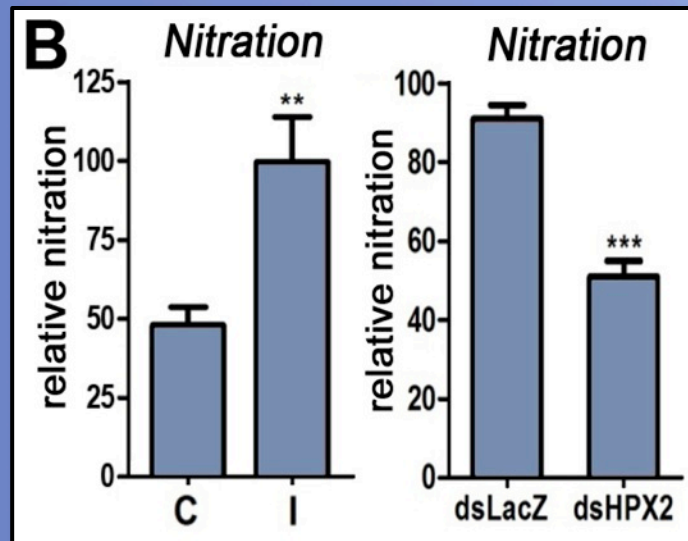
Han *et al.*, 2000



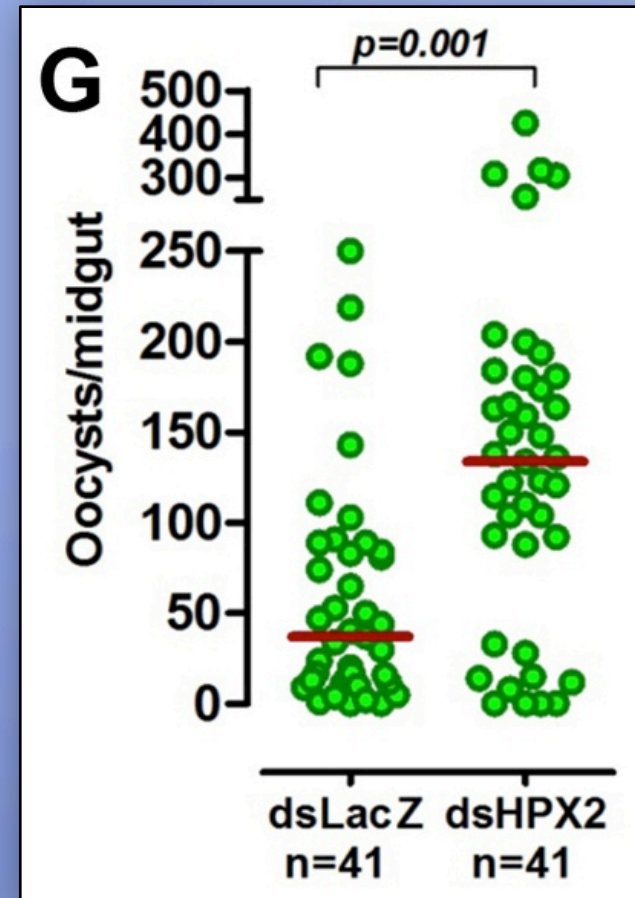
Kumar *et al.*, 2004



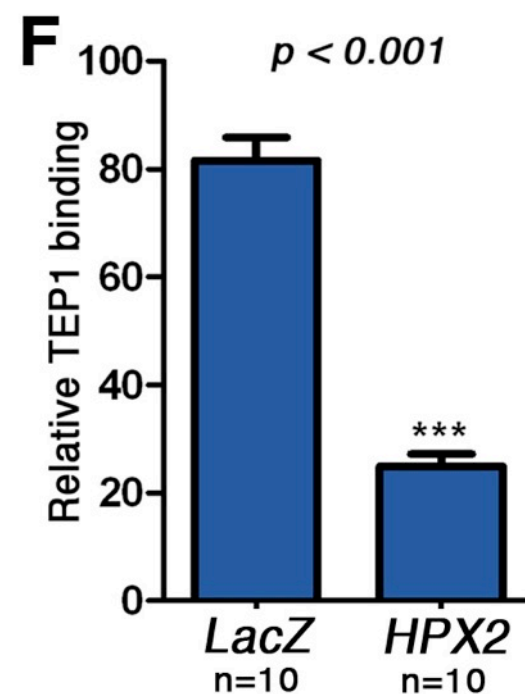
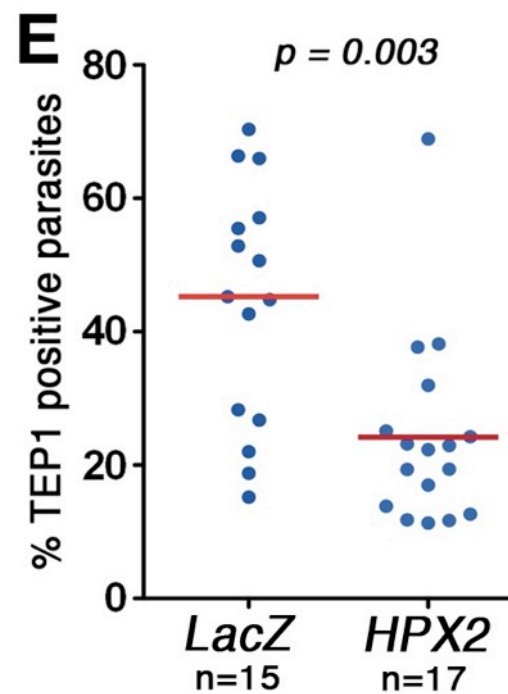
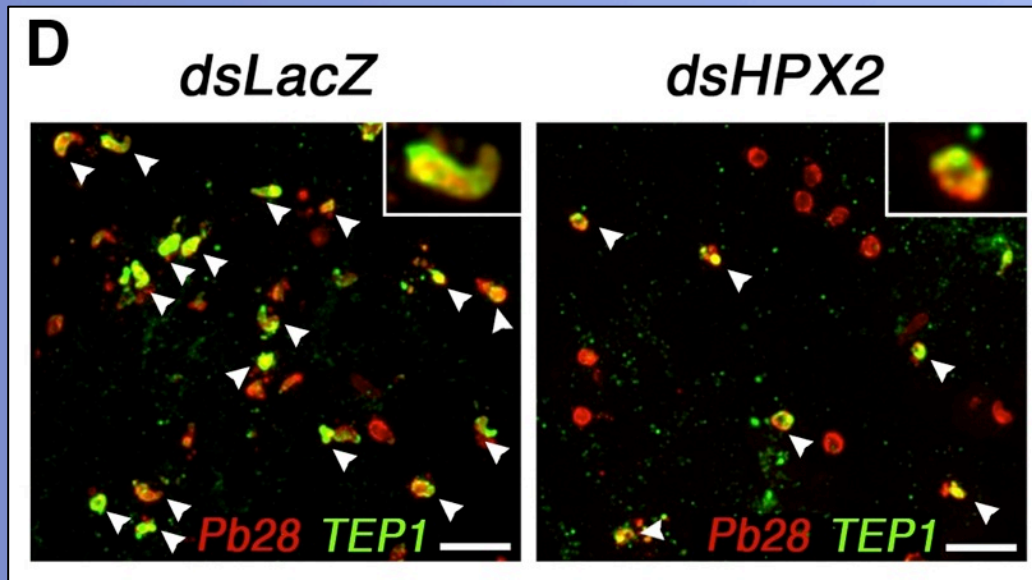
In vivo midgut nitration



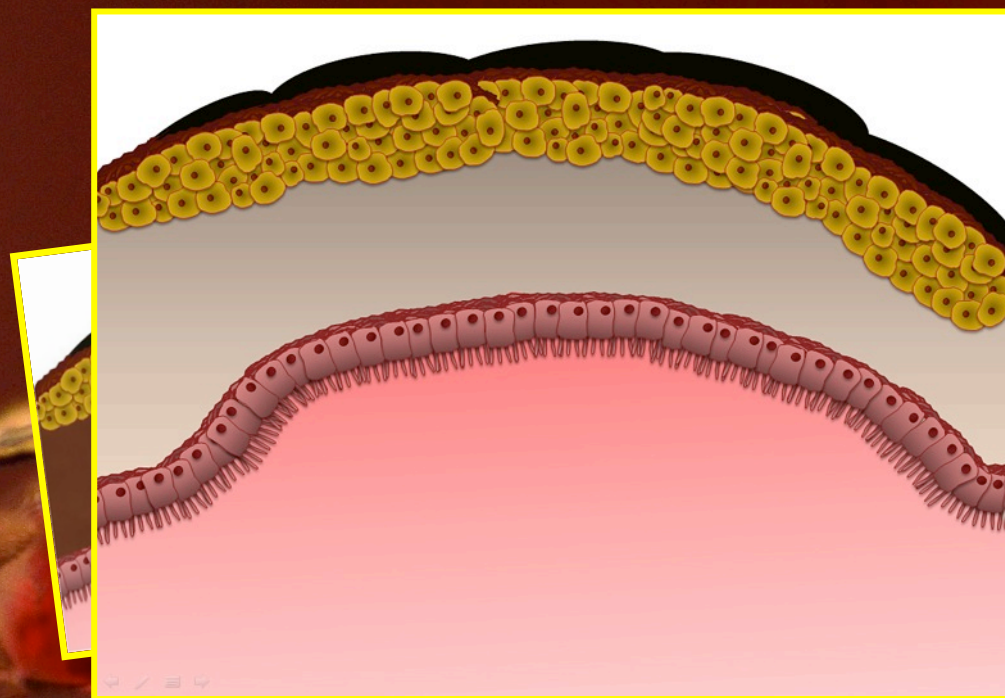
HPX2

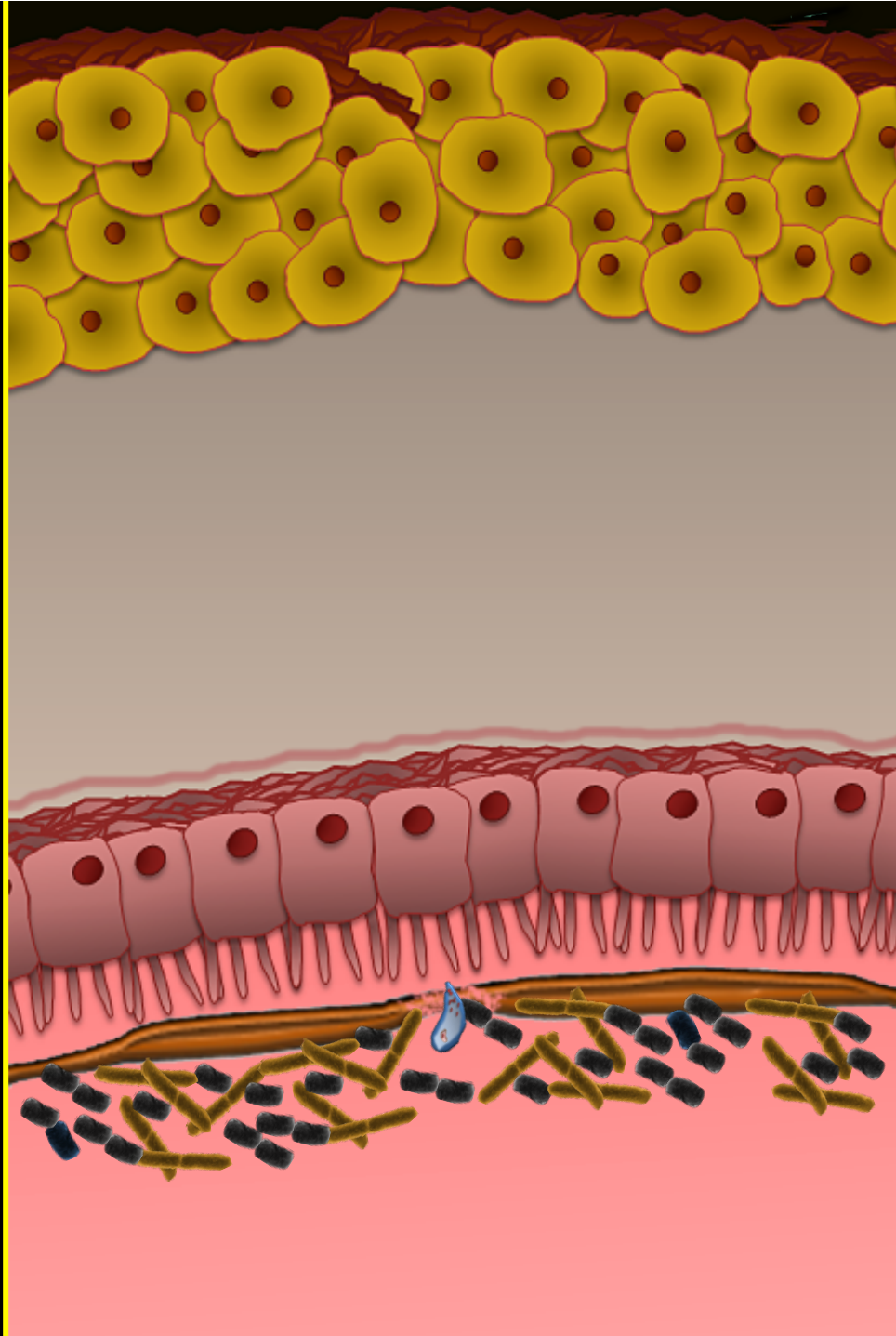


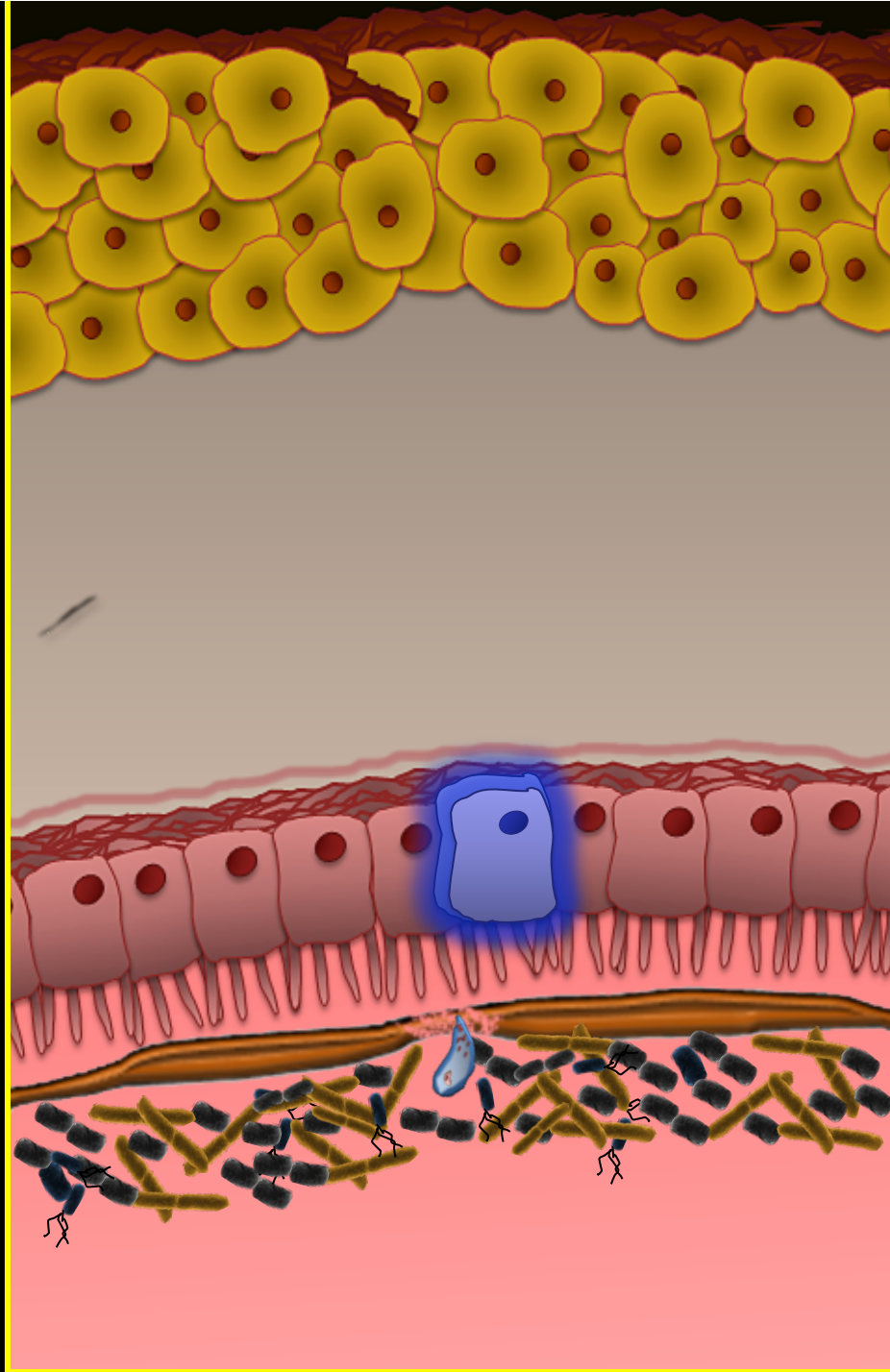
HPX2 mediates protein nitration and limits *Plasmodium* survival.

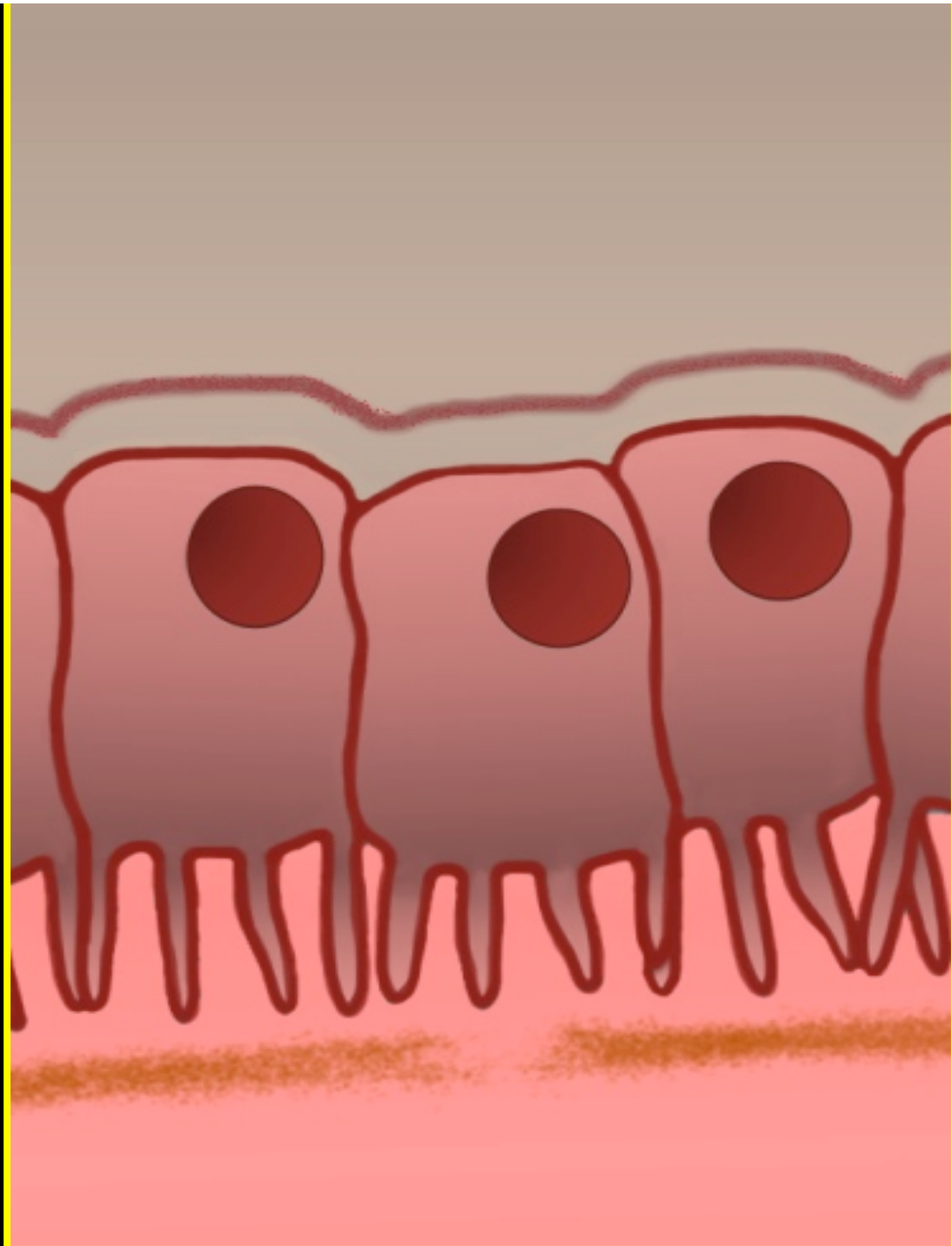


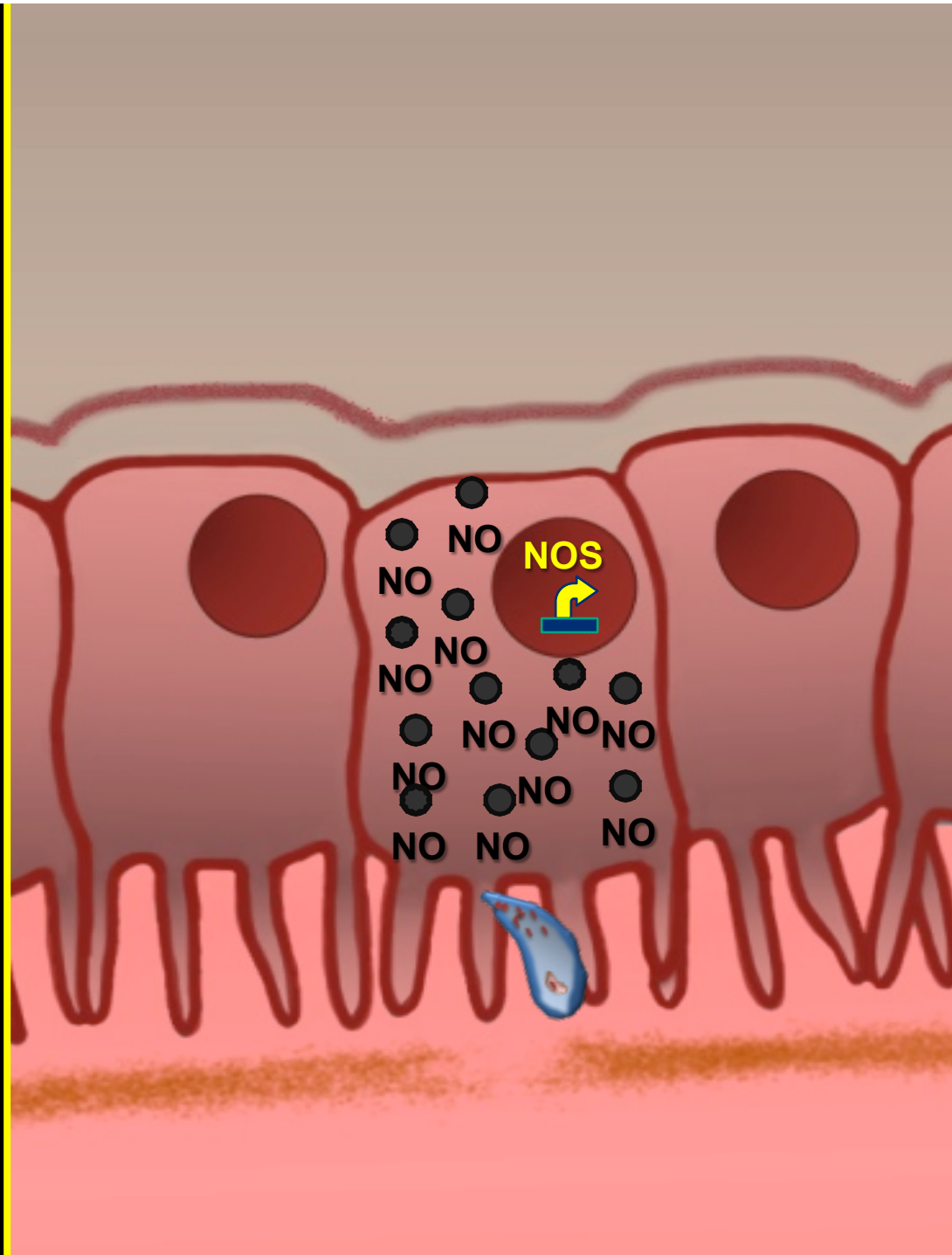


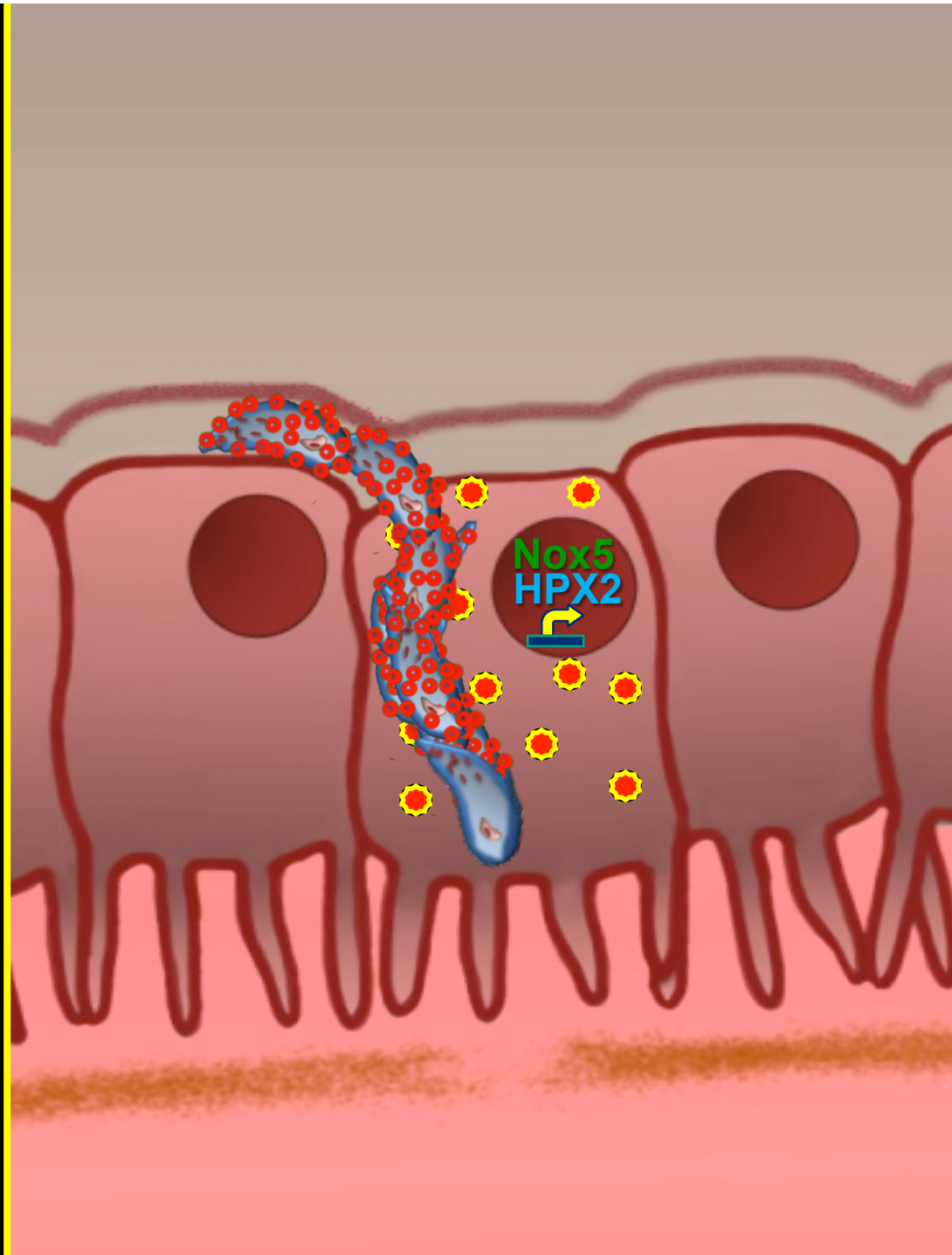


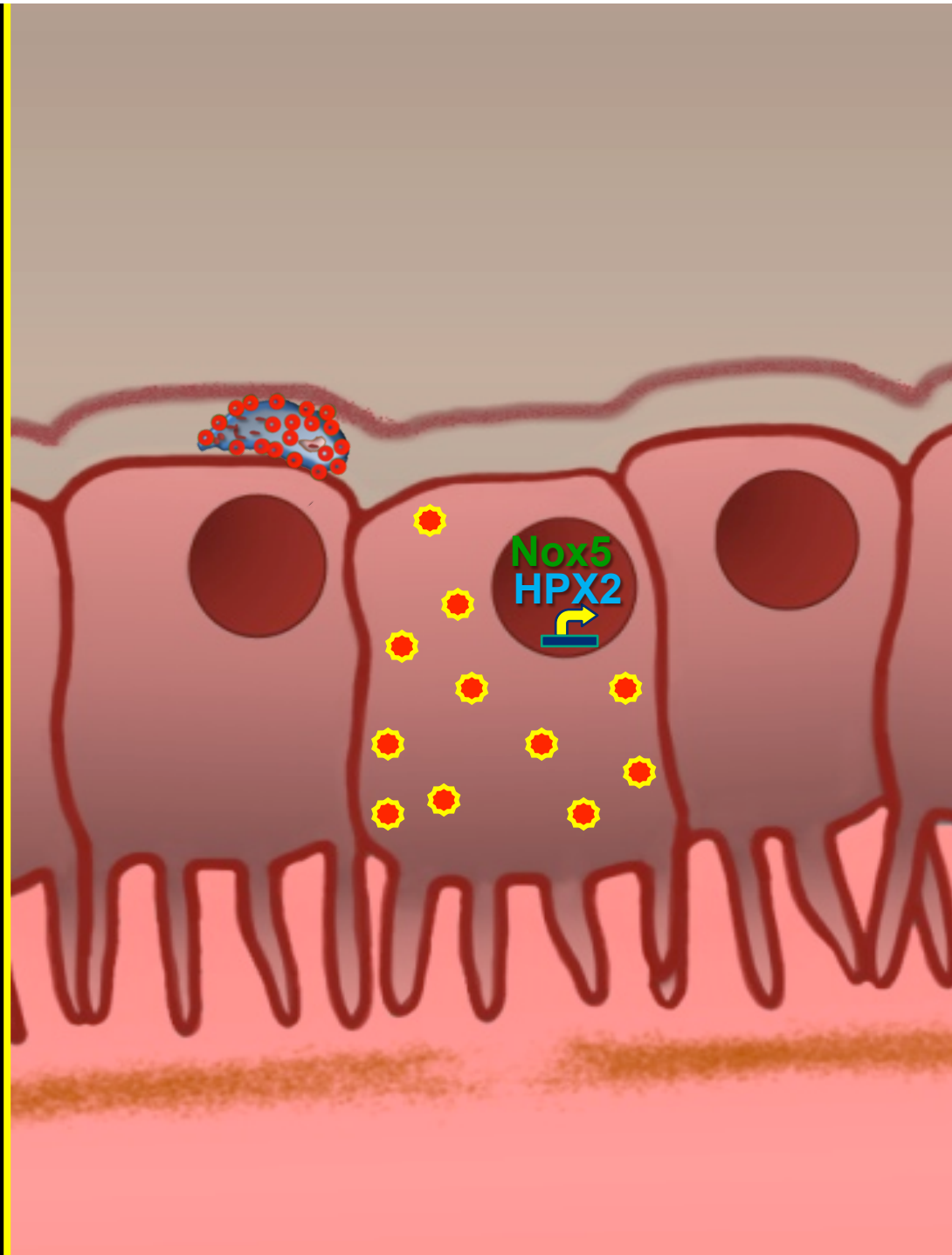


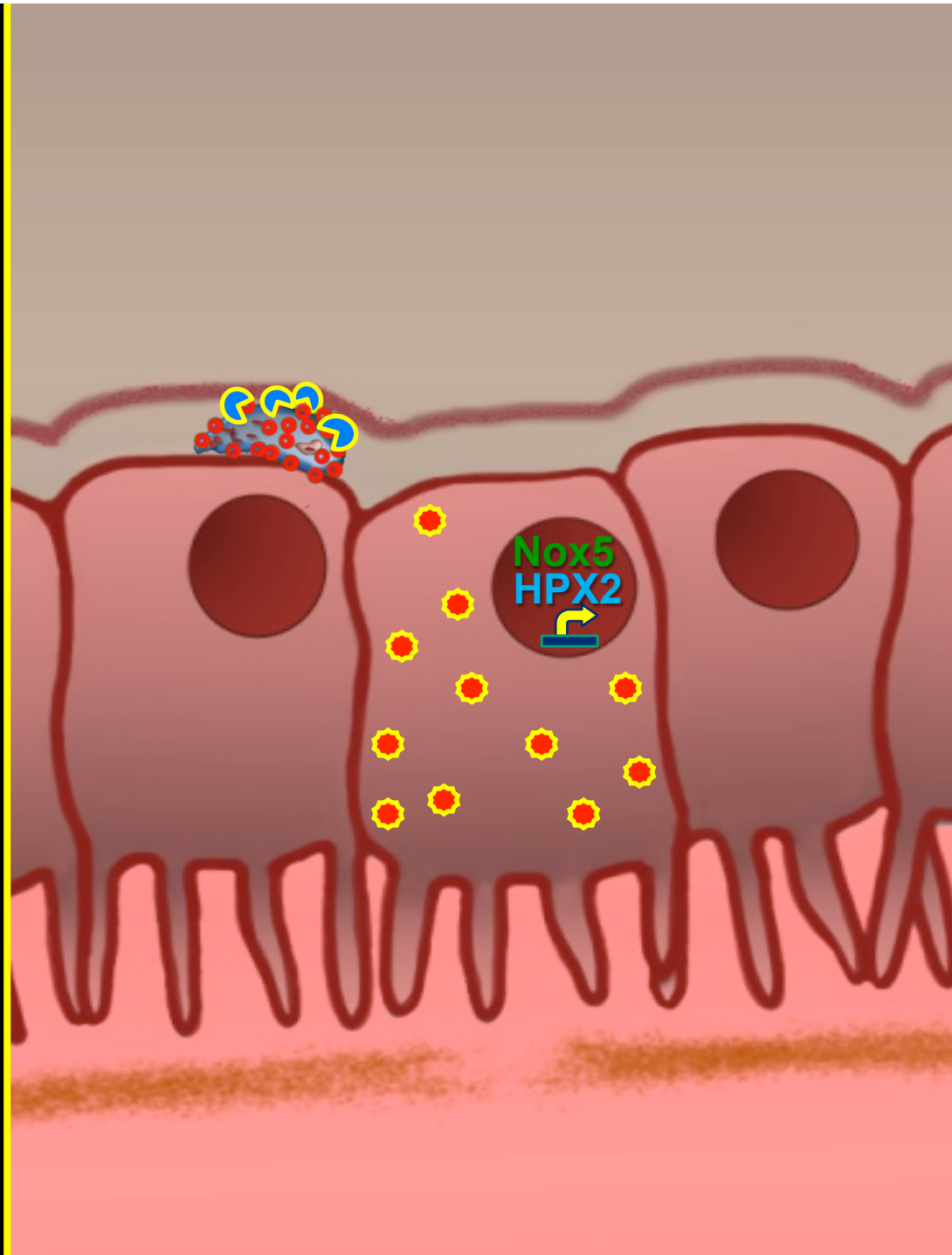




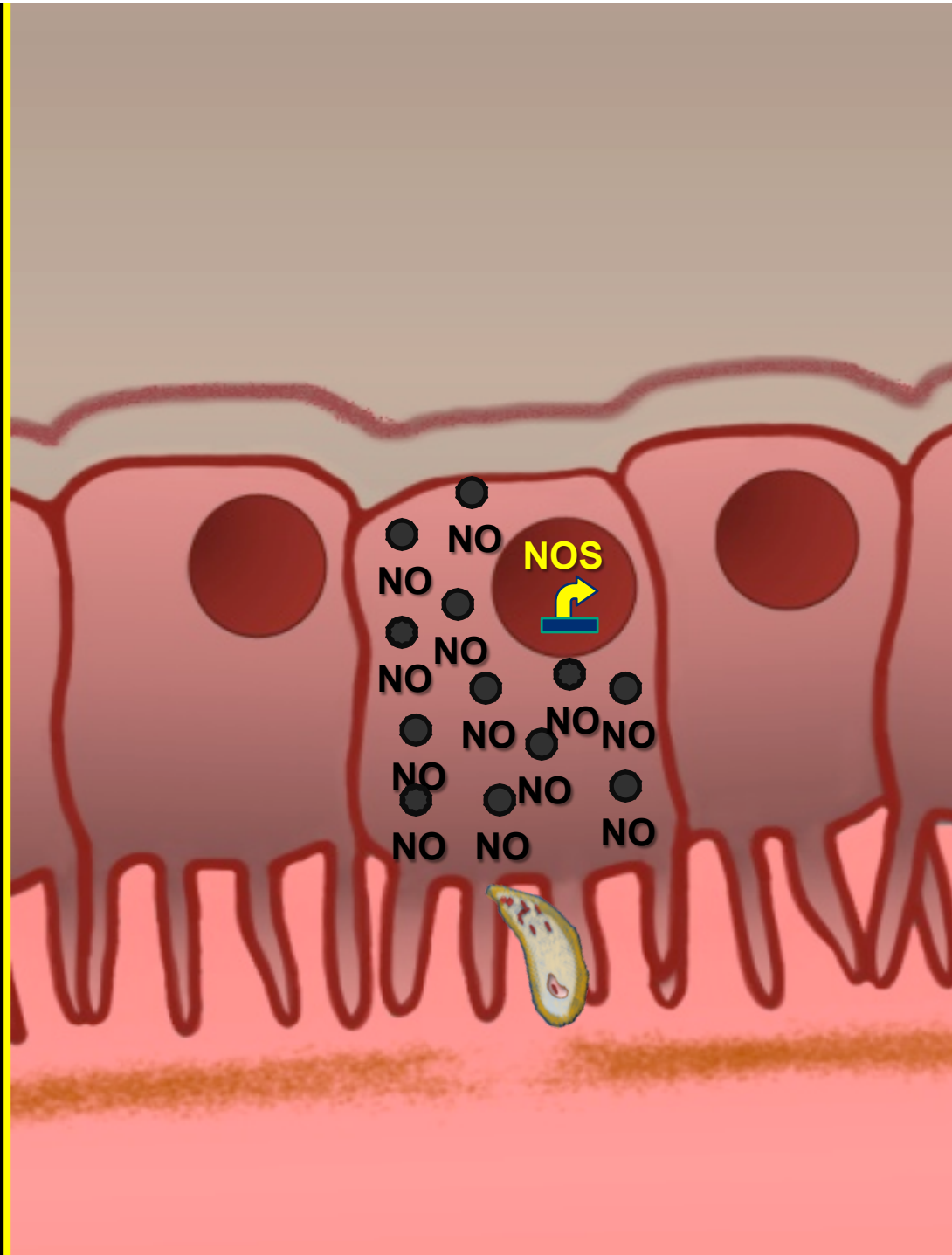


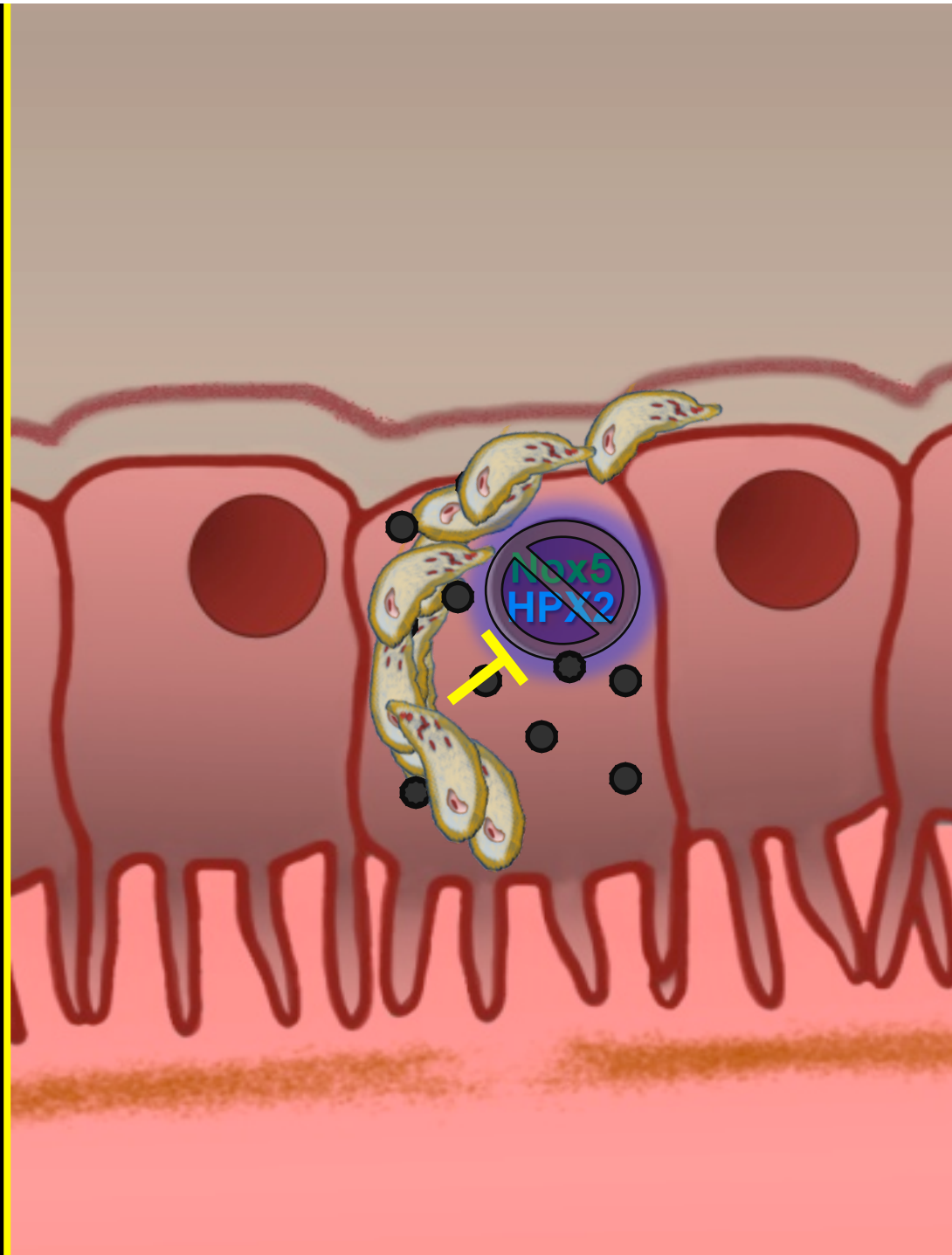


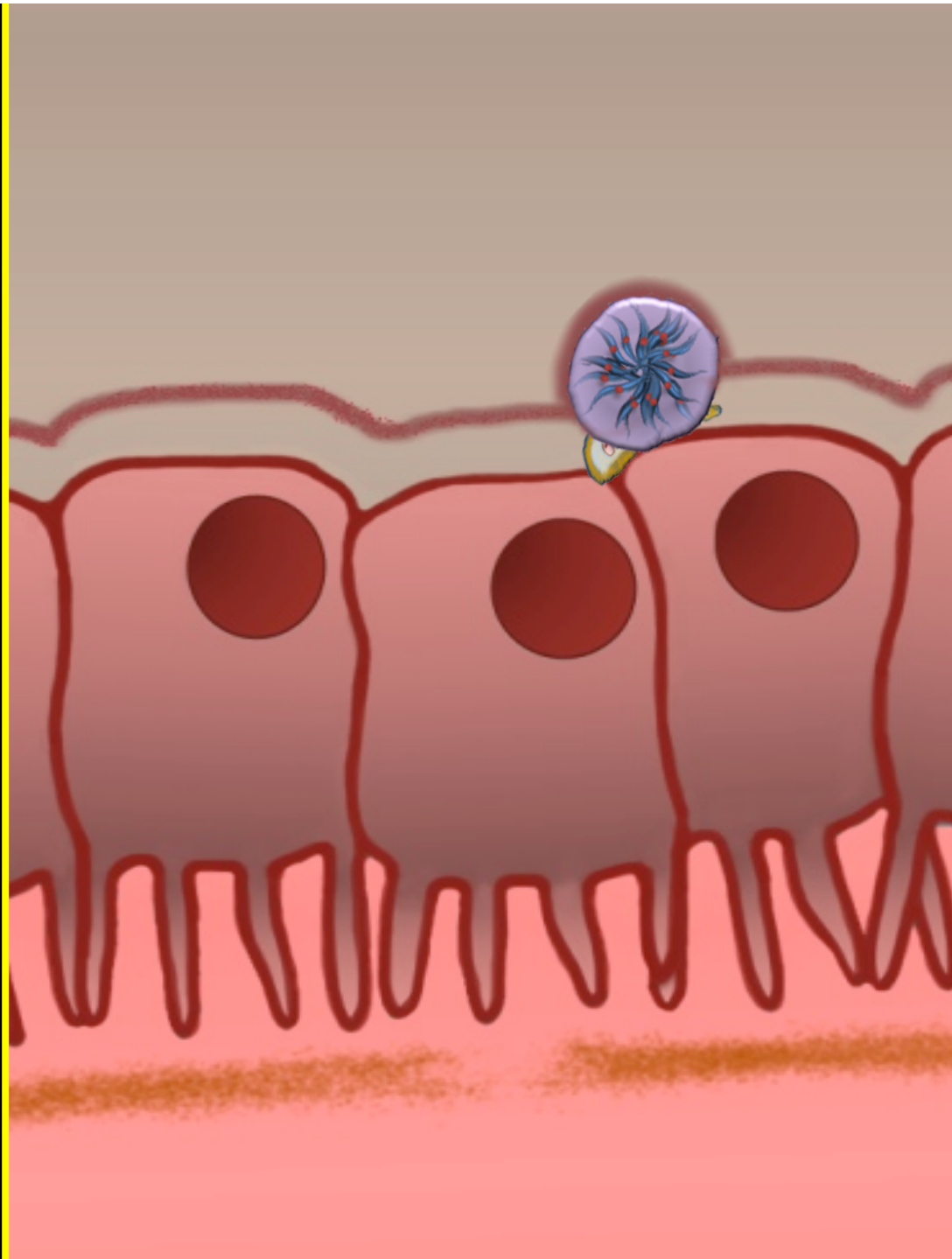




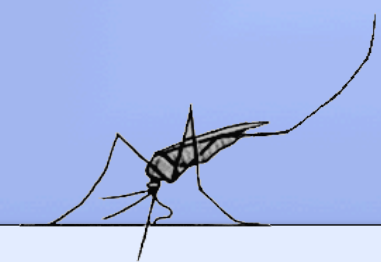










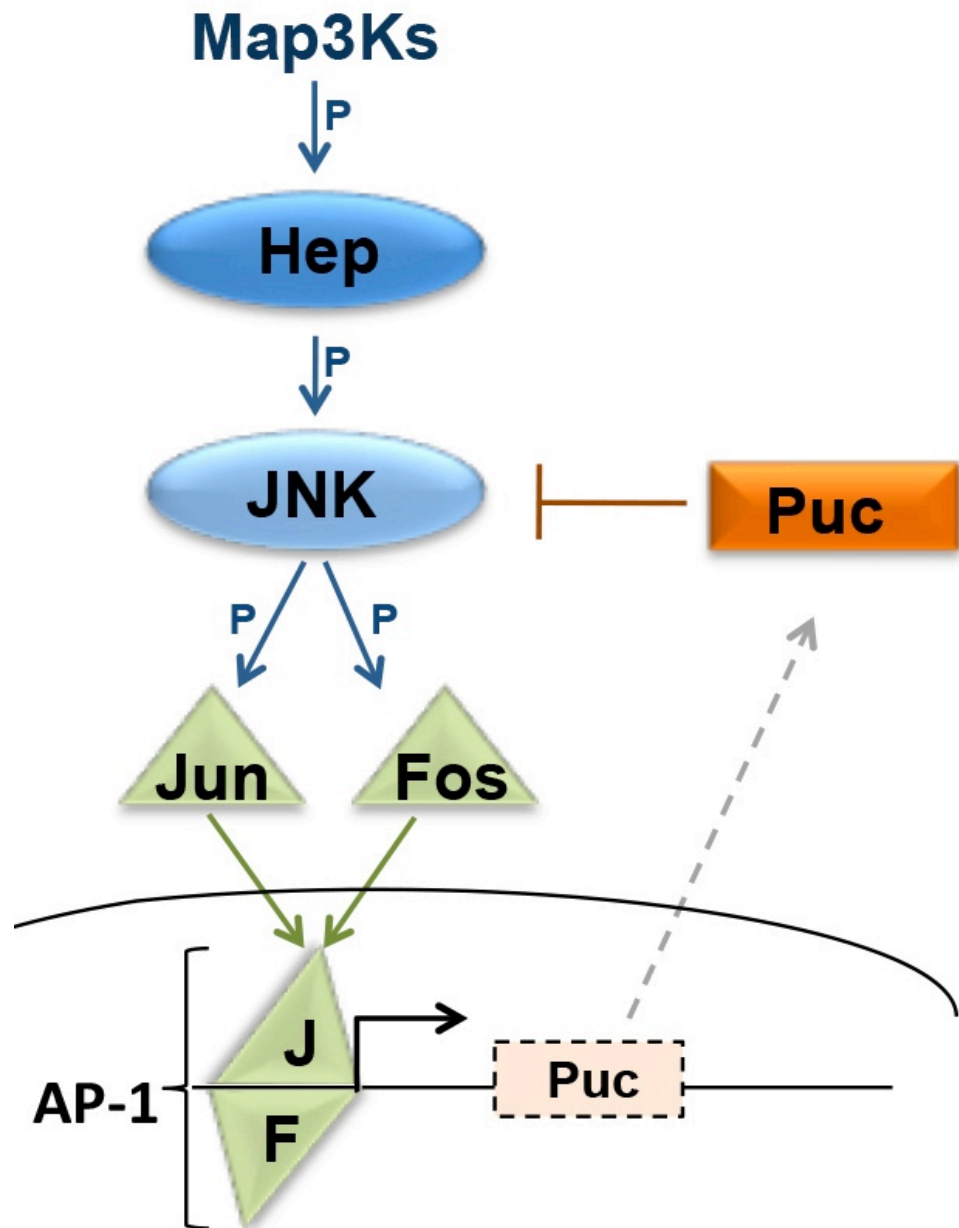


Outline

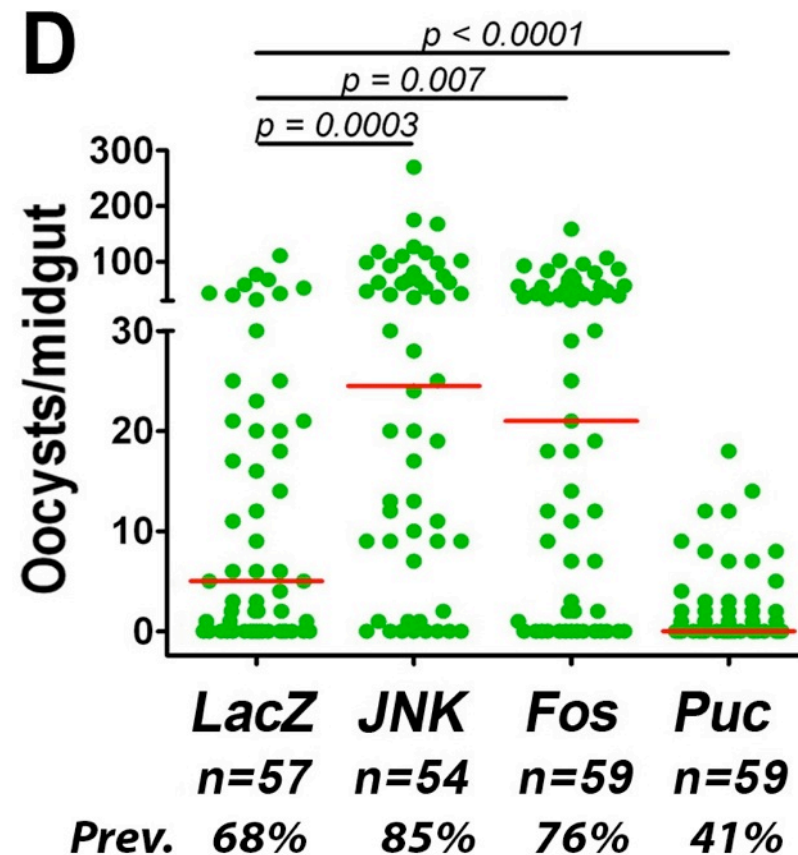
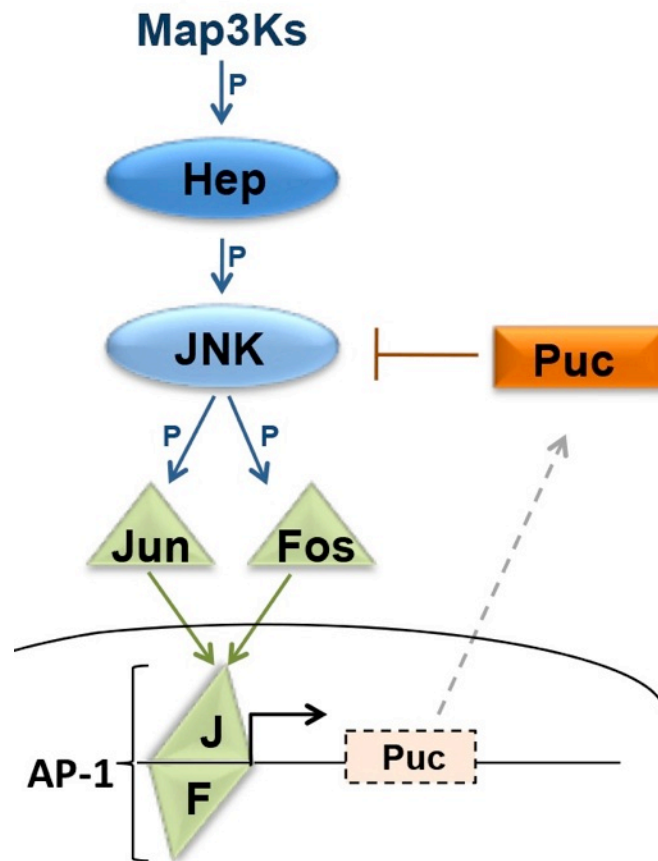
1. Epithelial Nitration and Complement Activation.
2. Participation of the JNK pathway in mosquito antiplasmodial immunity.
3. *Plasmodium falciparum* evasion of the mosquito immune system.

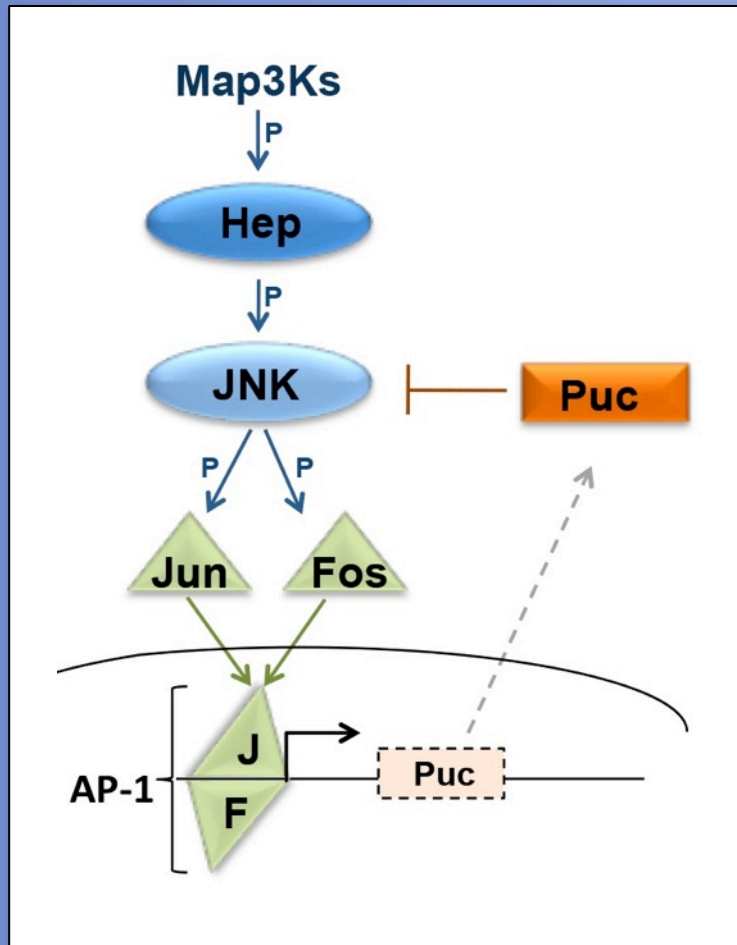
JNK Pathway

- *Development*
- *Immunity*
- *Apoptosis*
- *Stress response*



The JNK pathway mediates antiplasmodial responses to *P. berghei* infection.





JNK

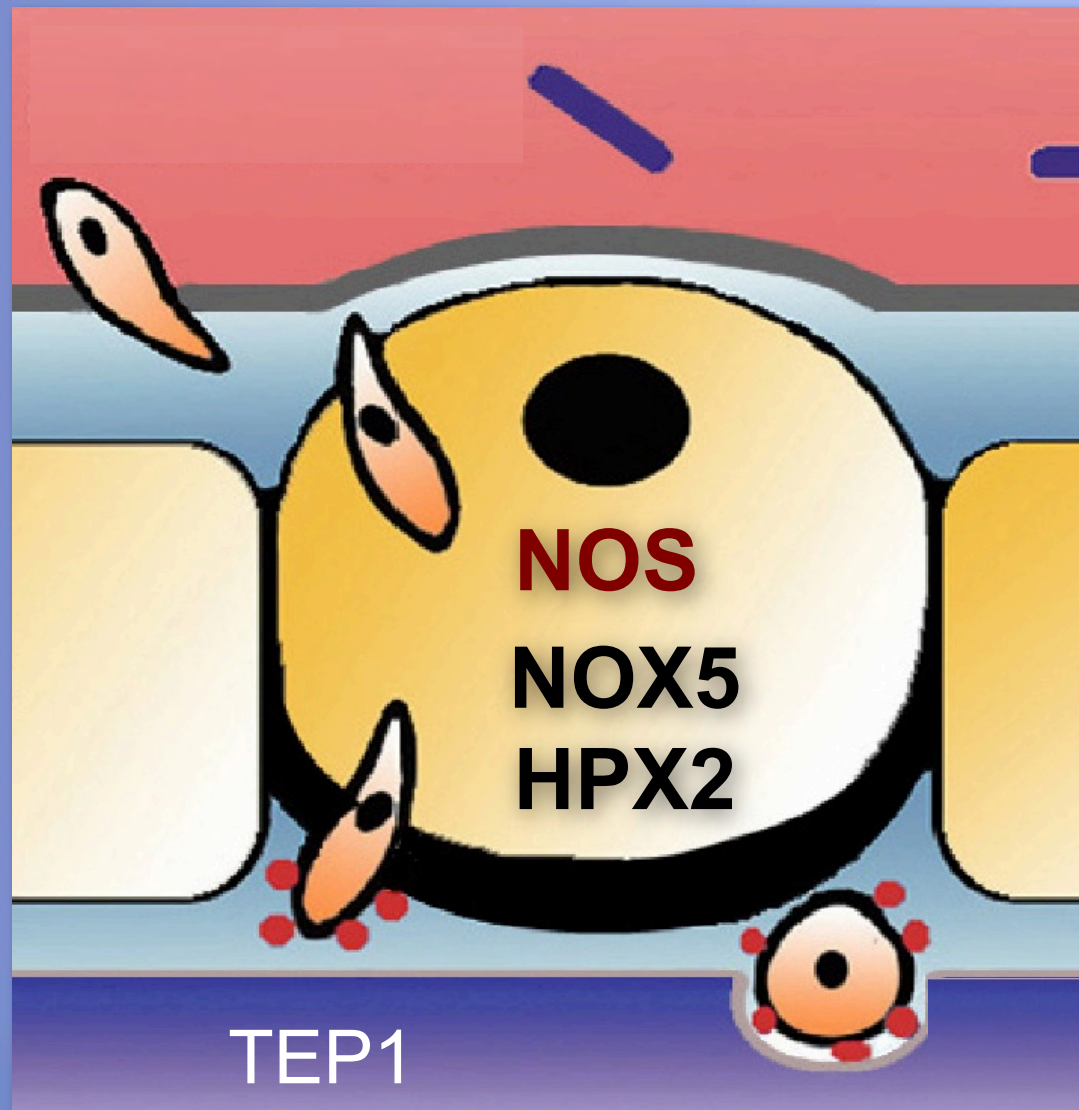
↓

NOX5 + HPX2

↓

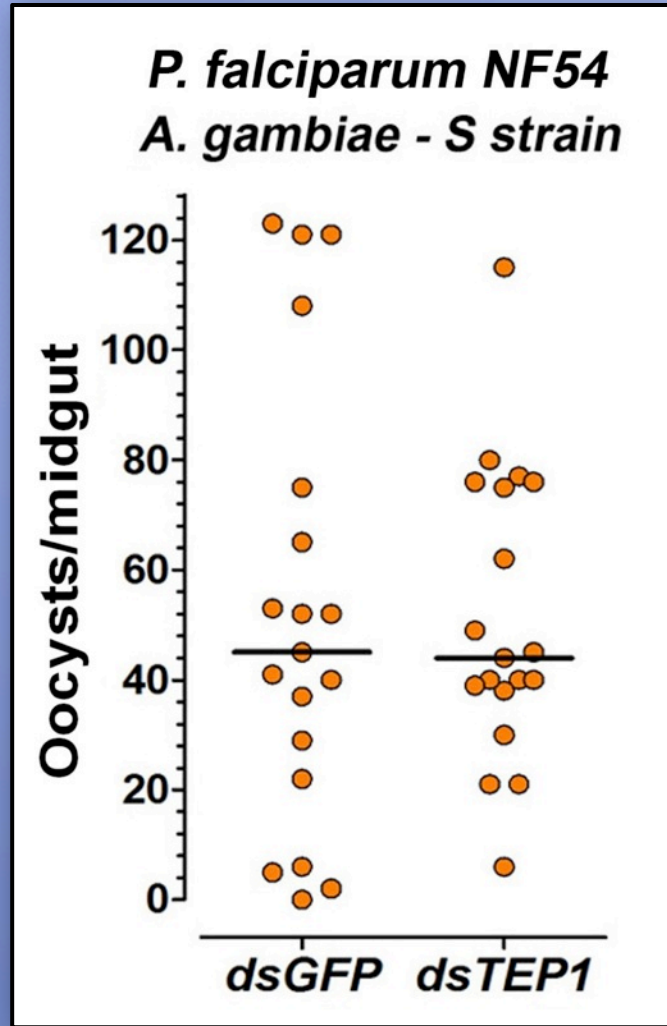
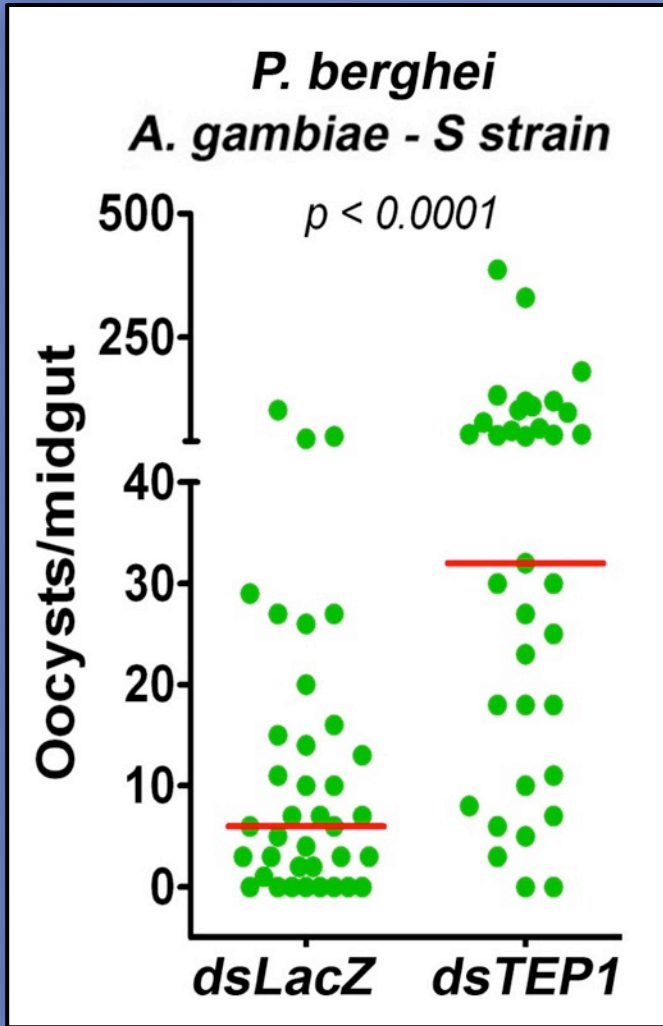
Nitration

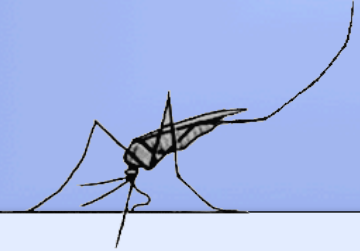
- The JNK pathway regulates the induction of HPX2 and NOX5 in response to ookinete midgut invasion.





TEP1-mediated lysis in *P. berghei* and *P. faciparum*

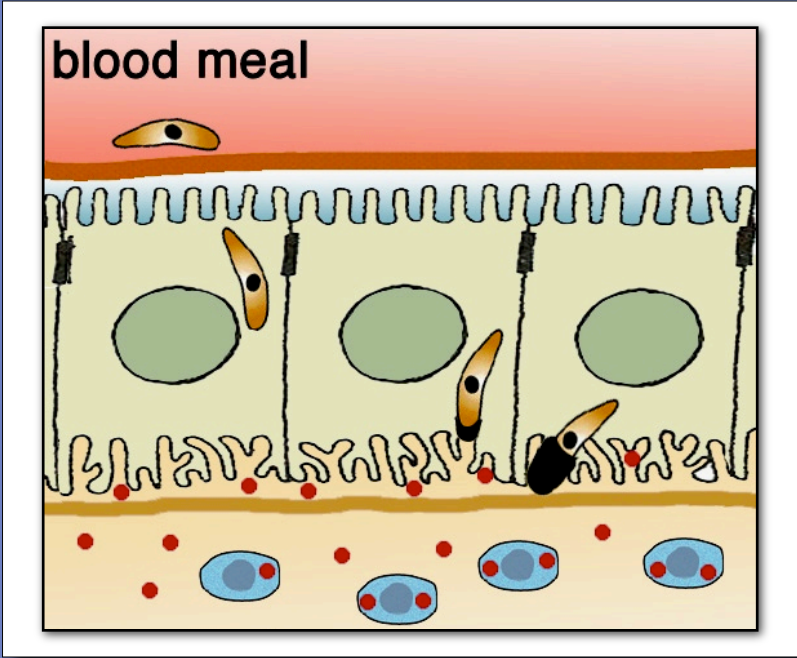




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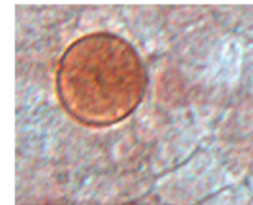
A. gambiae Refractory (R) strain



P. falciparum infections

African

GB4

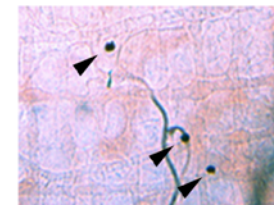


Scatter plot showing the relationship between Melanized parasites (x-axis) and Live oocysts (y-axis). The x-axis ranges from 0 to 80, and the y-axis ranges from 0 to 80. Data points are clustered near the origin, with a few points at higher values. The sample size $n = 32$ is indicated.

Parasite melanization 0 %

Brazilian

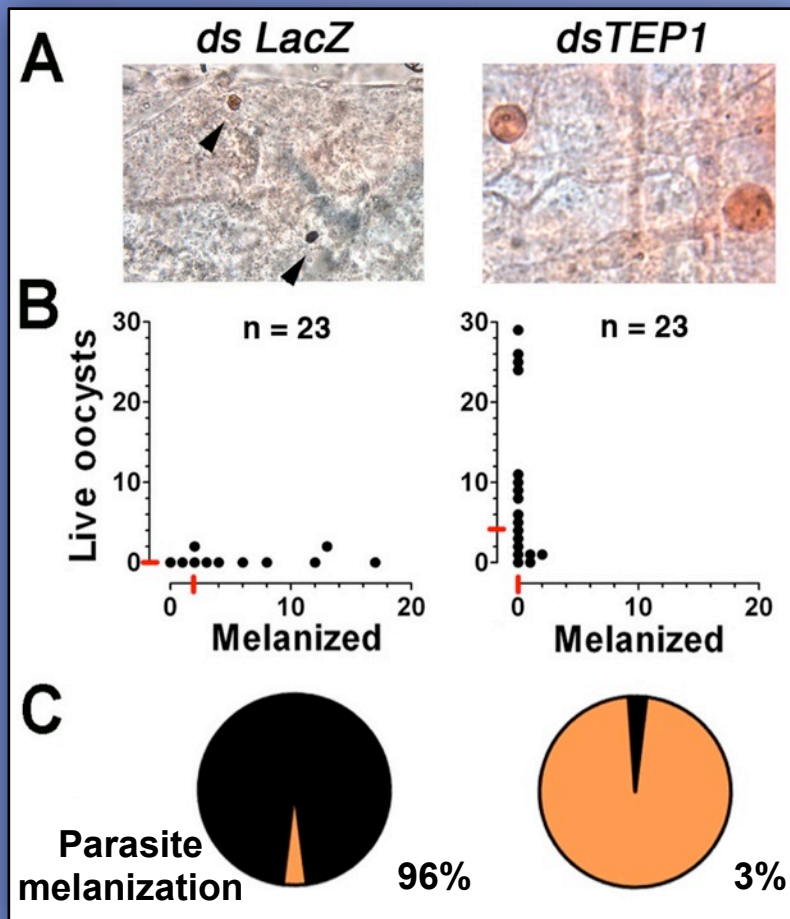
7G8



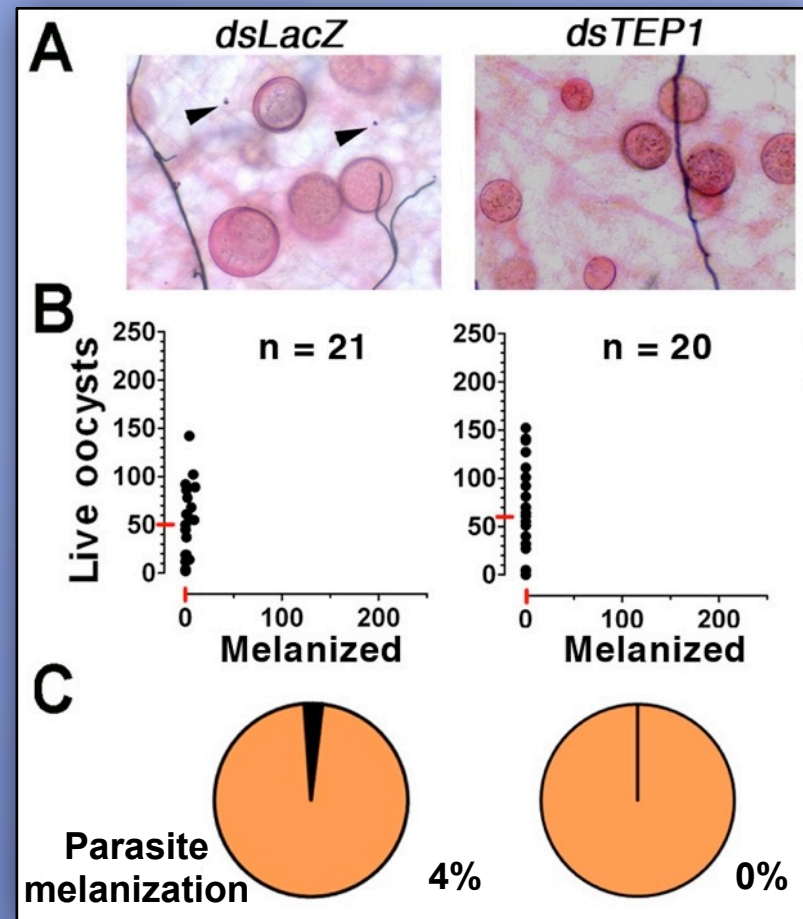
Dot plot showing the number of melanized parasites for 37 individuals. The y-axis ranges from 0 to 150. The x-axis is labeled 'Melanized parasites' and ranges from 0 to 80. Most individuals have 0 to 10 melanized parasites, with one individual having 60.

97 %

Pf 7G8 - Brazil

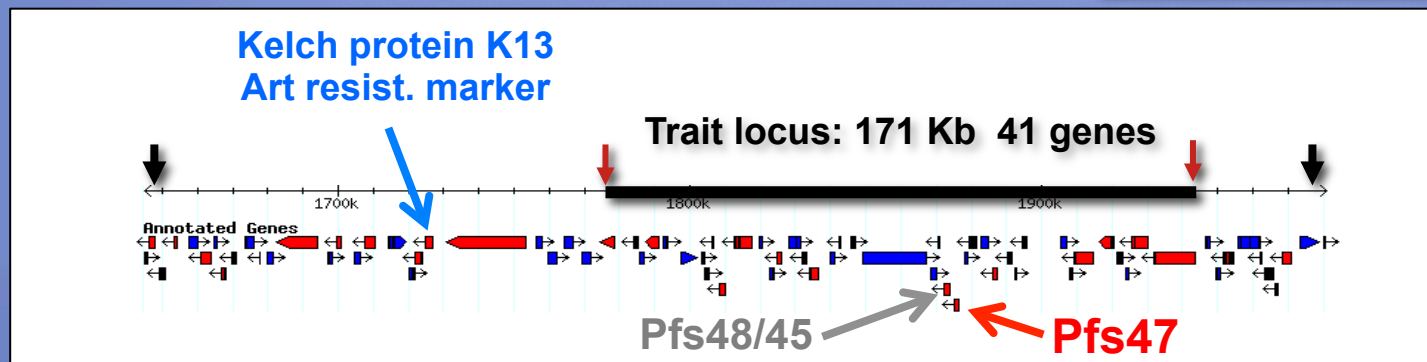
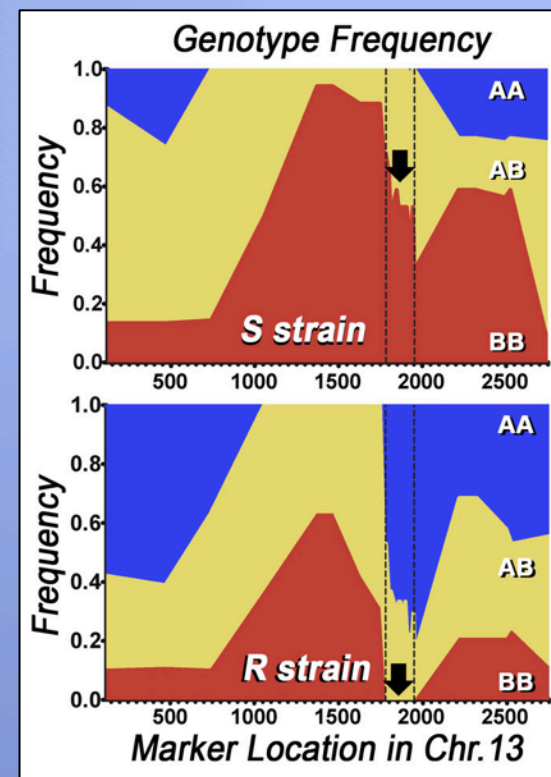
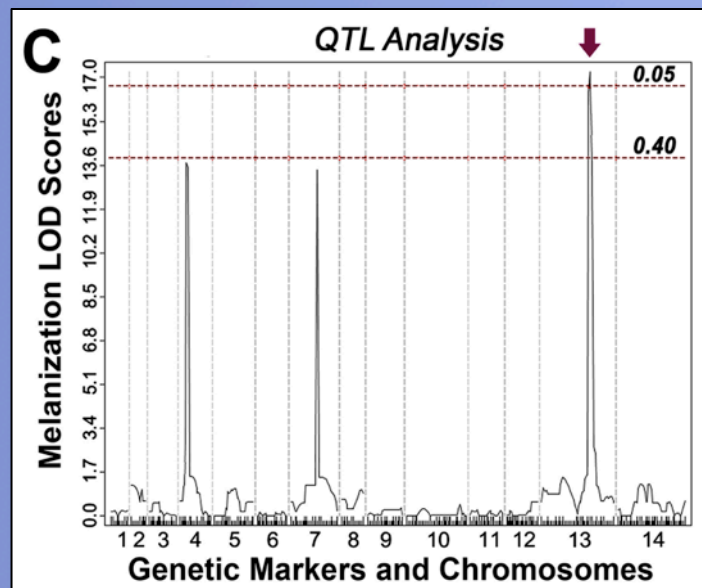
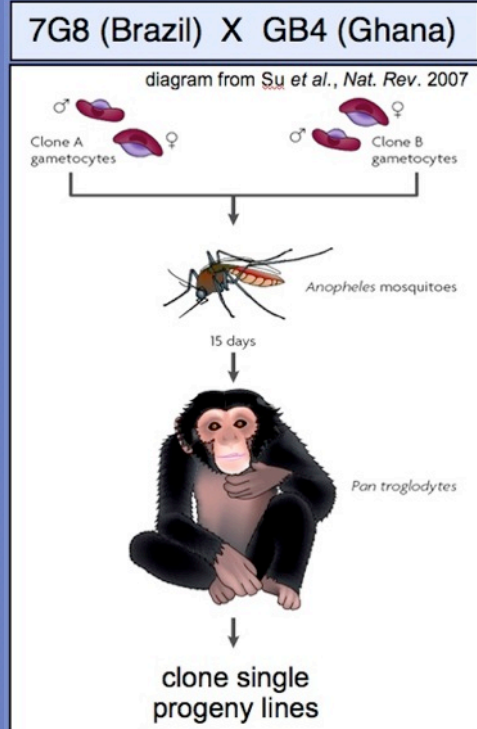


Pf NF54 - Africa

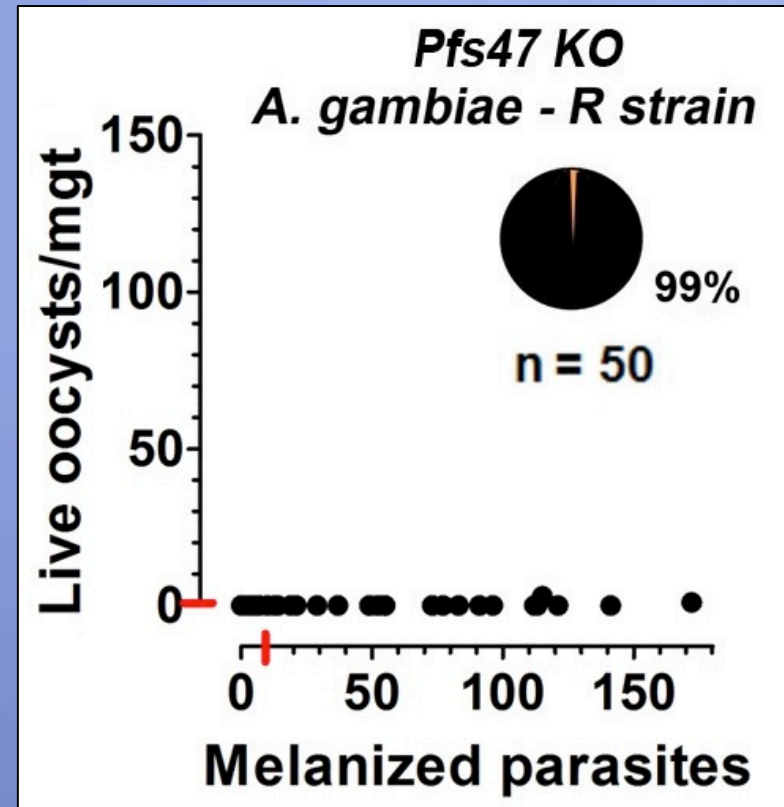
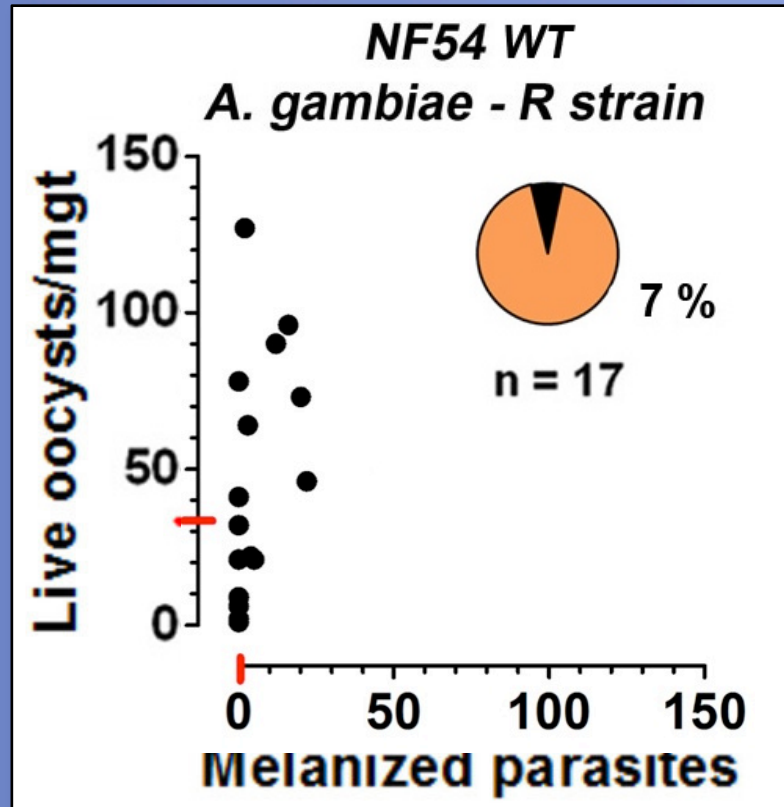


Immune evasion

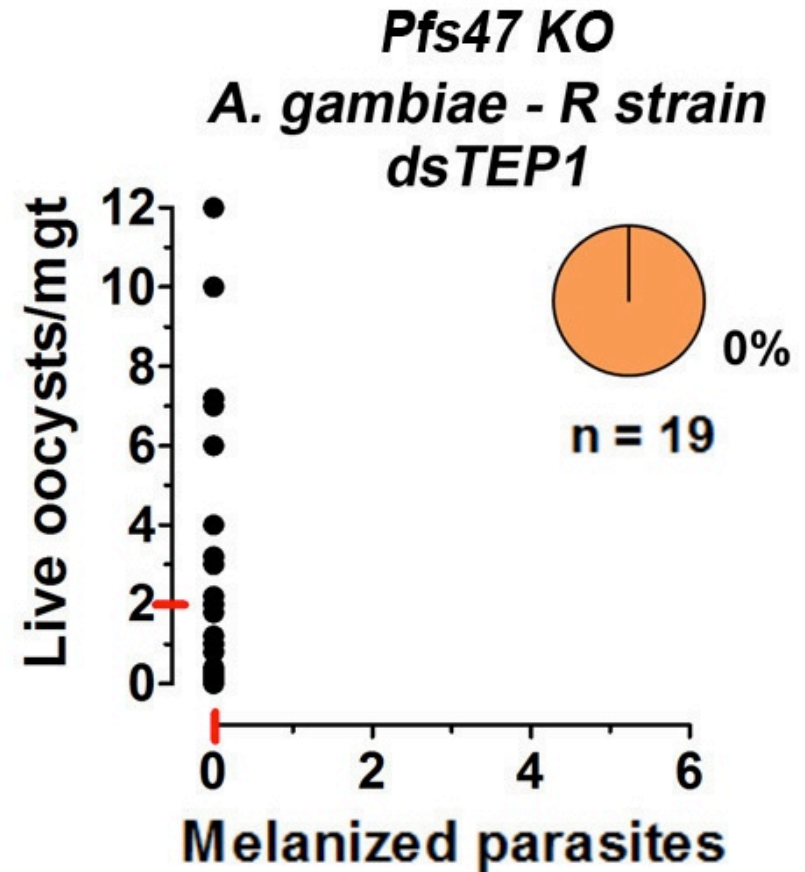
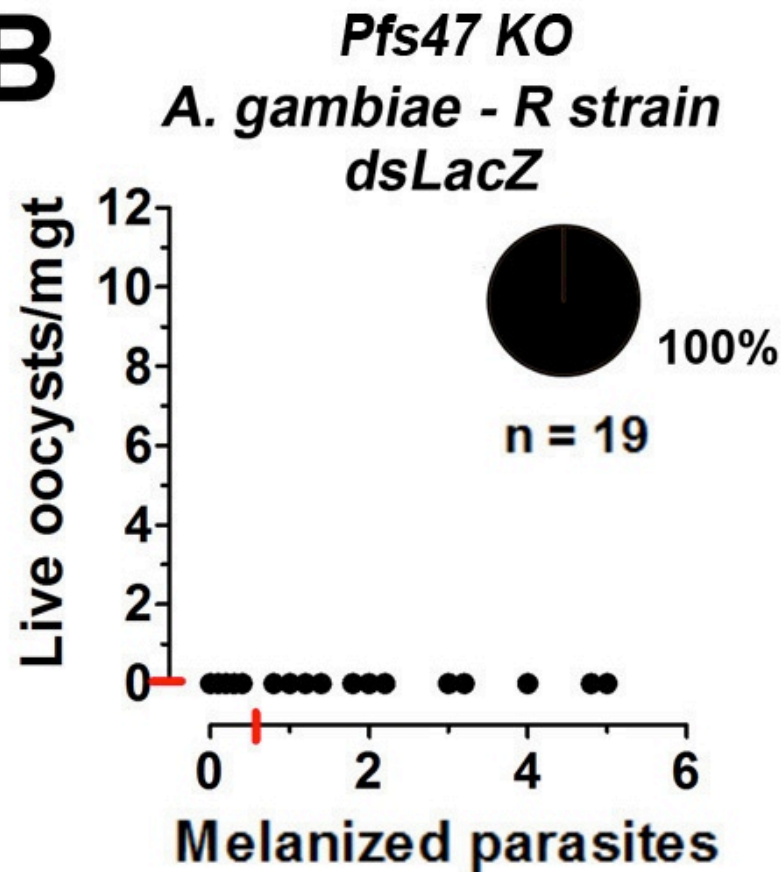
Identification of *P. falciparum* gene(s) that allow some African strains to escape melanization in the *An. gambiae* refractory strain



Pfs47 KO phenotype in NF54 background

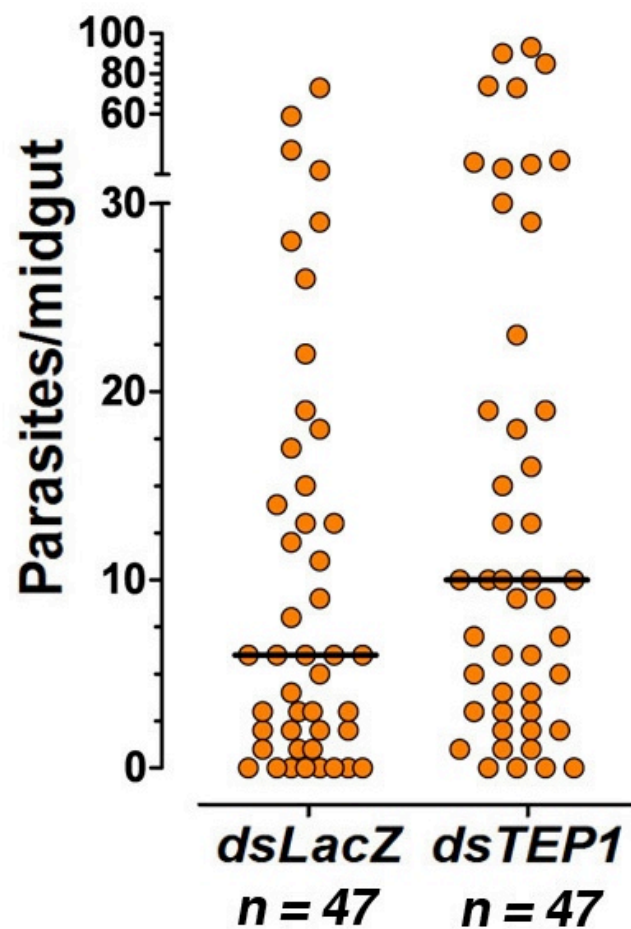


B

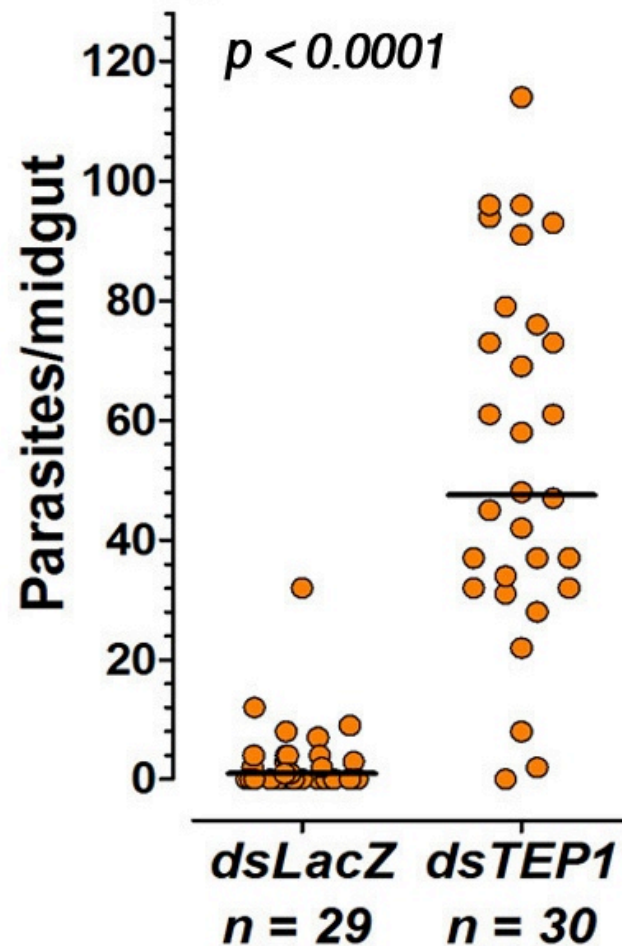


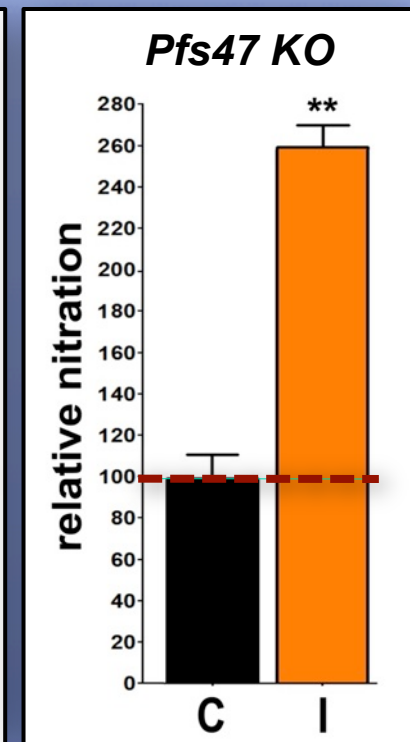
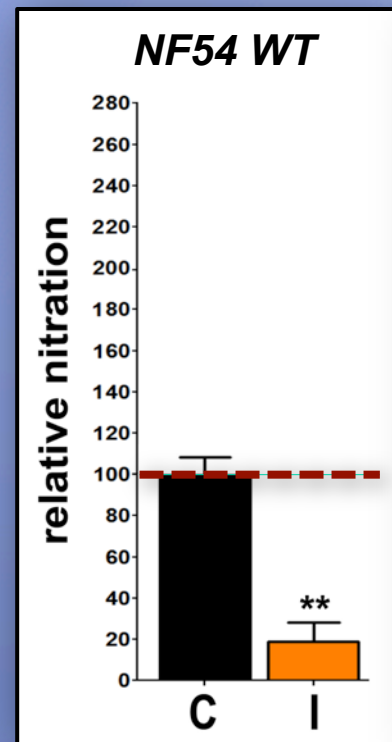
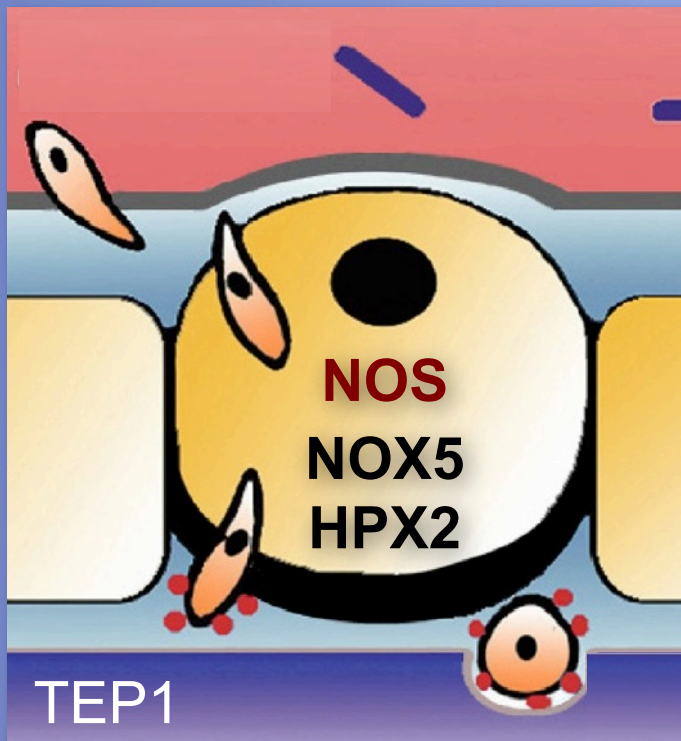
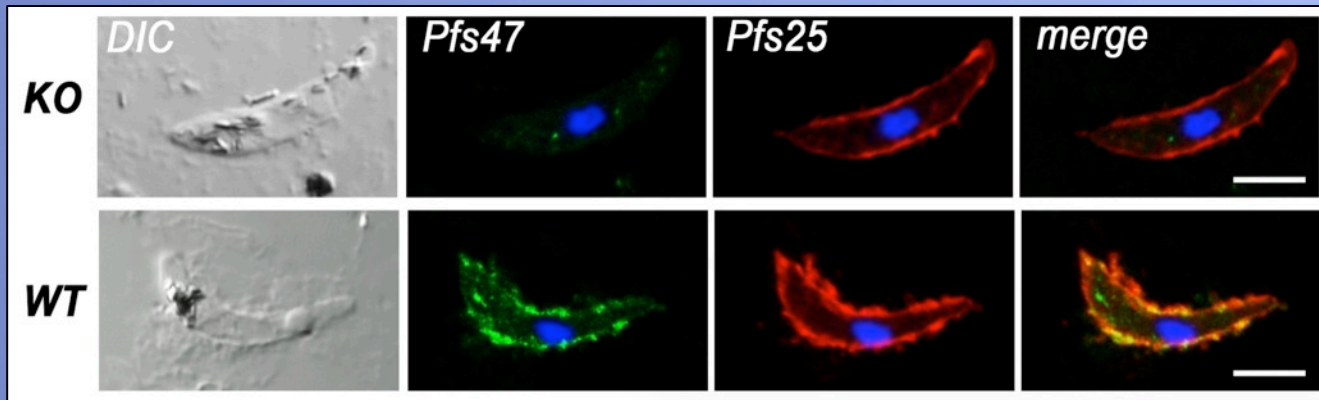
C

NF54 WT
***A. gambiae* - S strain**



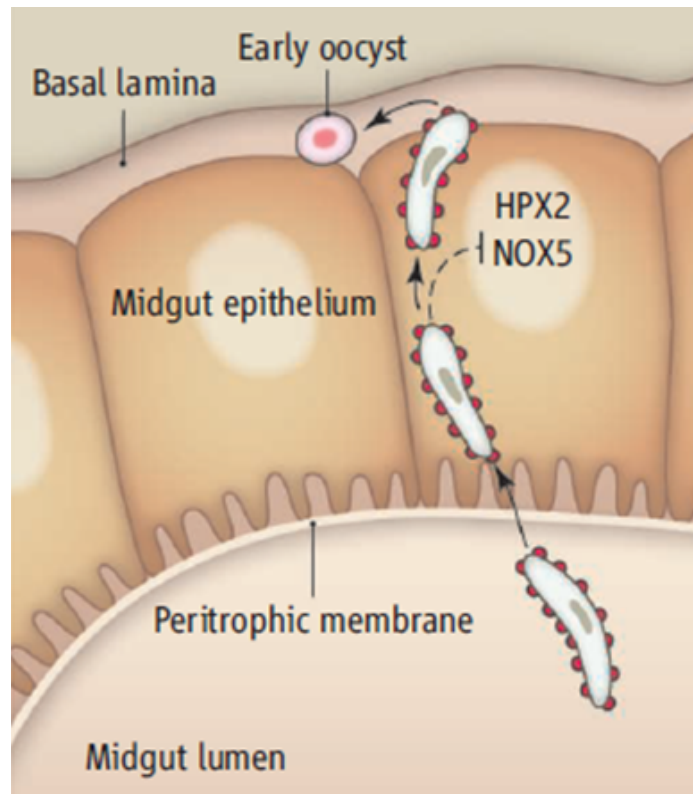
Pfs47 KO
***A. gambiae* - S strain**



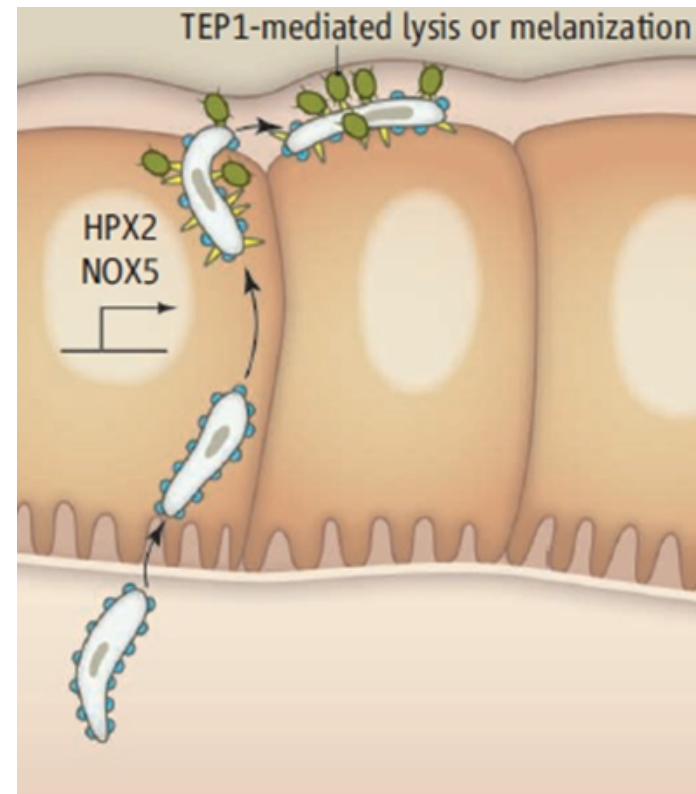


Hypothesis: *P. falciparum* evades the *A. gambiae* immune system by disrupting *JNK* signaling.

NF54 wt

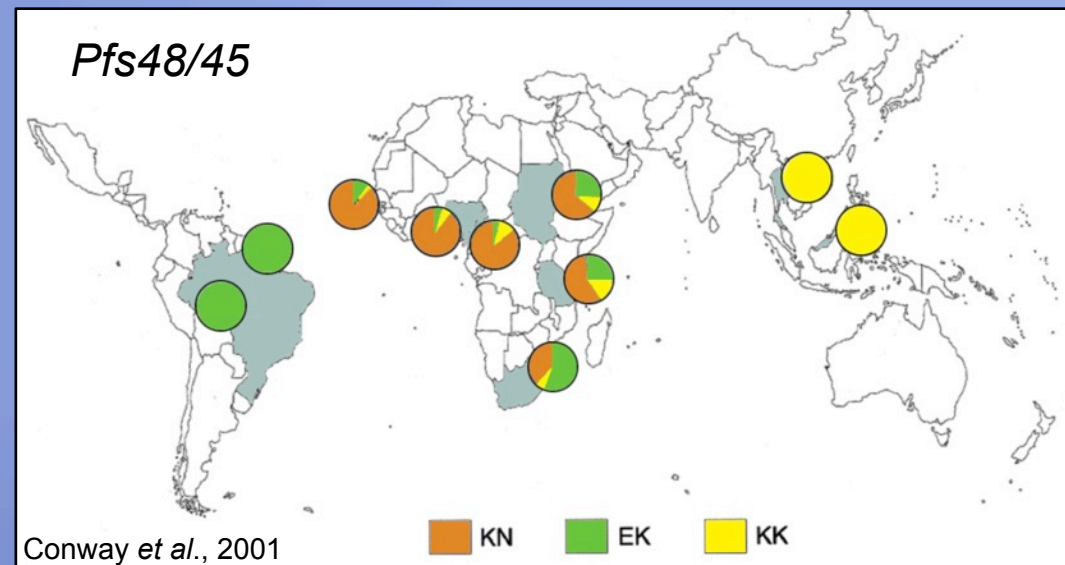


NF54 Pfs47 ko



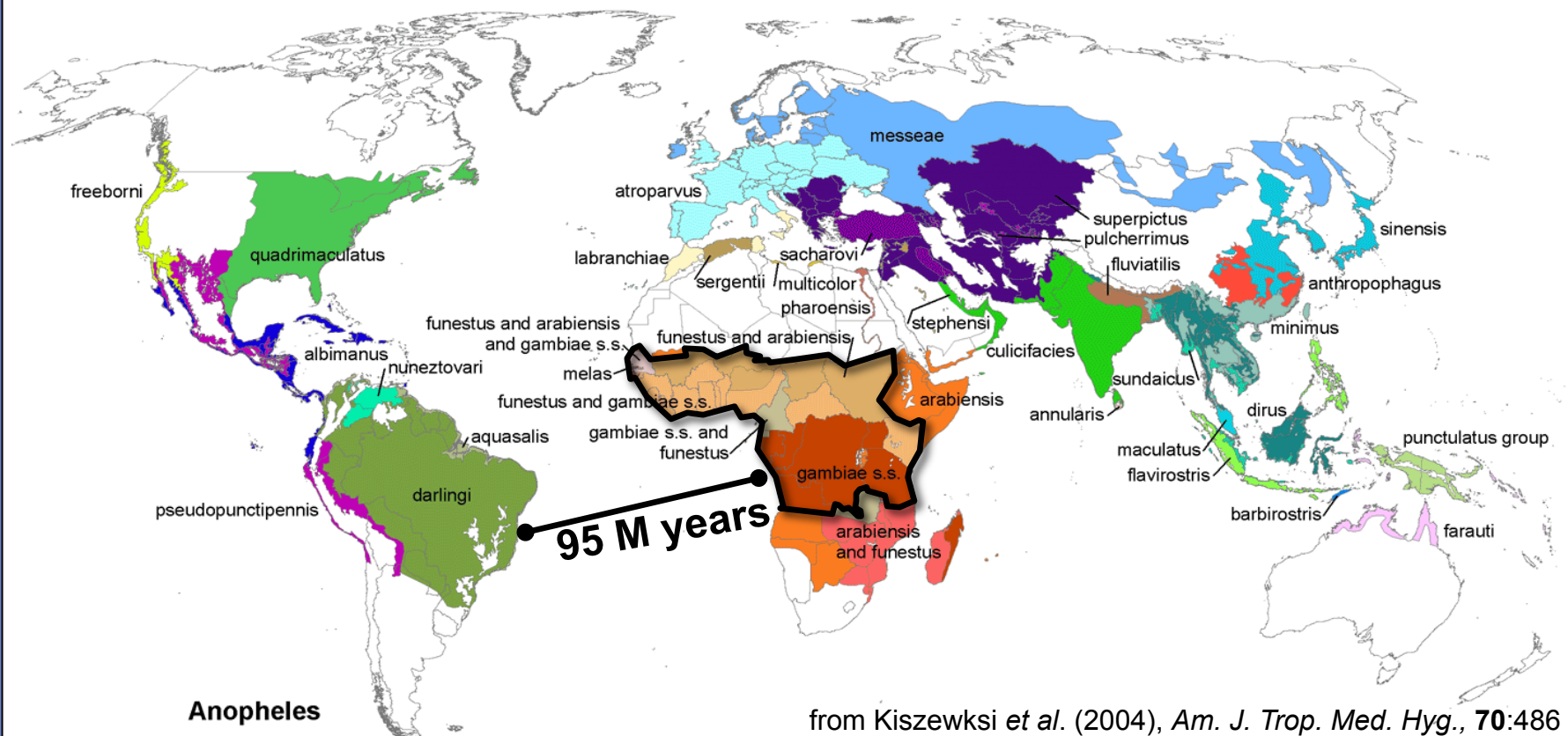
	<i>Pfs48/45</i>	<i>Pfs47</i>
Americas	OGG0000	00000A00T0TCT00000
	OGG0000	00000A00T0TCT00000
	OGG0000	00000A00T0TCT00000
	OGG0000	00000A00T0TCT00000
	OGG0000	00000A00T0TCT00000
	OGG0000	00000A00T0TCT00000
	OGG0000	00000A00T0TCT00000
	OGG0000	00000A00T0TCT00000
	OGG0000	00000A00T0TCT00000
	OGG0000	00000A00T0TCT00000
Africa	OGG0000	T0000A000000T0T0A0
	OOGA0A0	0A0A0A0ATA00T0T000
	00000000	00000A00000000000000
	OGG0000	00000A00T0TCT00000
	00000000	T0000A00000000000000
	OGG0000	T0000A00000000000000
	0000A00	00000A000000T0T000
	OGG0000	T0000A00000000000000
	OGGOA00	T0000A00000000000000
	OOGA0A0	00C00A00T000T0000T
Asia	0000A00	0000TA000000T00000
	OOGA0A0	0A0A0A0ATA00T0T000
	OOGA0A0	0A0A0A0ATA00T0T000
	OOGA0A0	0A000A0ATA00T0T000
	OOGA0A0	0A0A0A0ATA00T0T000
	OOGA0A0	0A000A0ATA00T0T000
	OOGA0A0	0A000A0ATA00T0T000
	OOGA0A0	0A000A0ATA00T0T000
	OOGA0A0	0A0A0A0ATA00T0T000
	OOGA0A0	0A0A0A0ATA00T0T000
	OOGA0A0	0A0A0A0ATA00T0T000
	OOGA0A0	0A0A0A0ATA00T0T000
	OOGA0A0	0A0A0A0ATA00T0T000
	OOGA0A0	0A0A0A0ATA00T0T000
	OOGA0A0	0A0A0A0ATA00T0T000
	OOGA0A0	0A0A0A0ATA00T0T000
	OOGA0A0	0A0A0A0ATA00T0T000
	OGG000A	0000TA000000T00000

Extreme geographical fixation of
Pfs47 and *Pfs48/45* variants



Hypothesis: The geographic structure of *Pfs47* alleles is determined by parasite selection by the mosquito vectors.

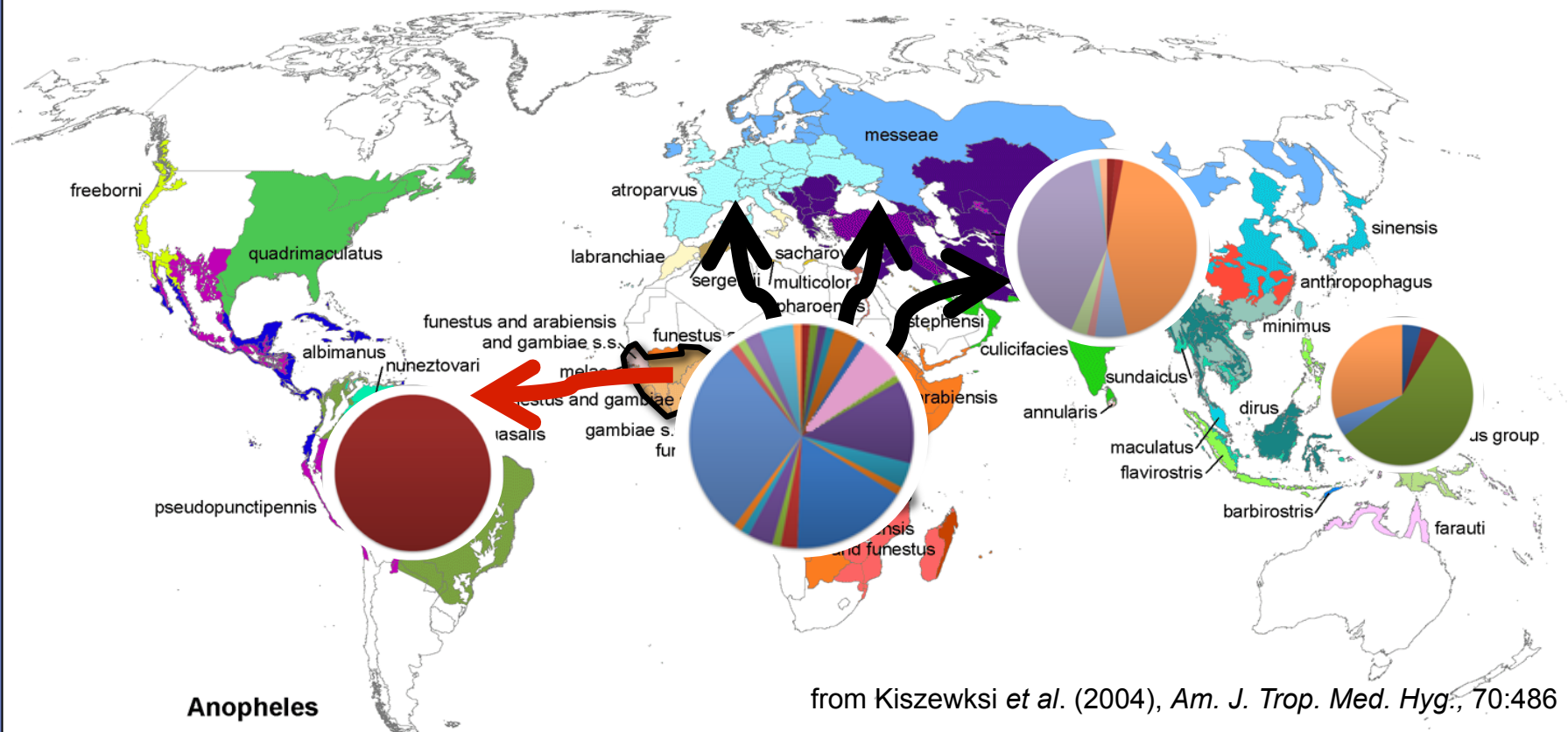
Geographic distribution of *Anopheles* spp.



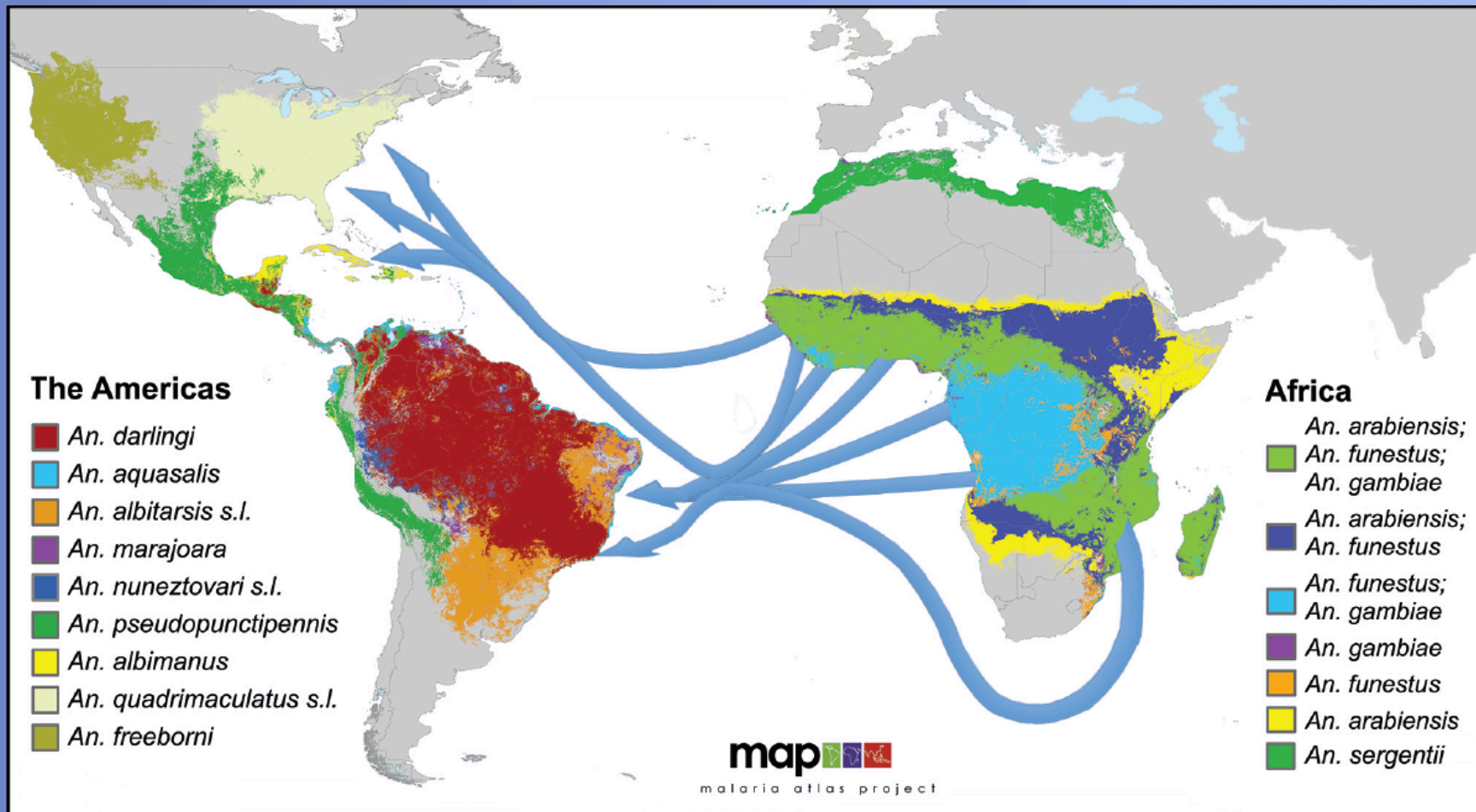
from Kiszewski *et al.* (2004), *Am. J. Trop. Med. Hyg.*, **70**:486

Geographic distribution of 30 *Pfs47* haplotypes identified
in 178 *P. falciparum* human isolates.

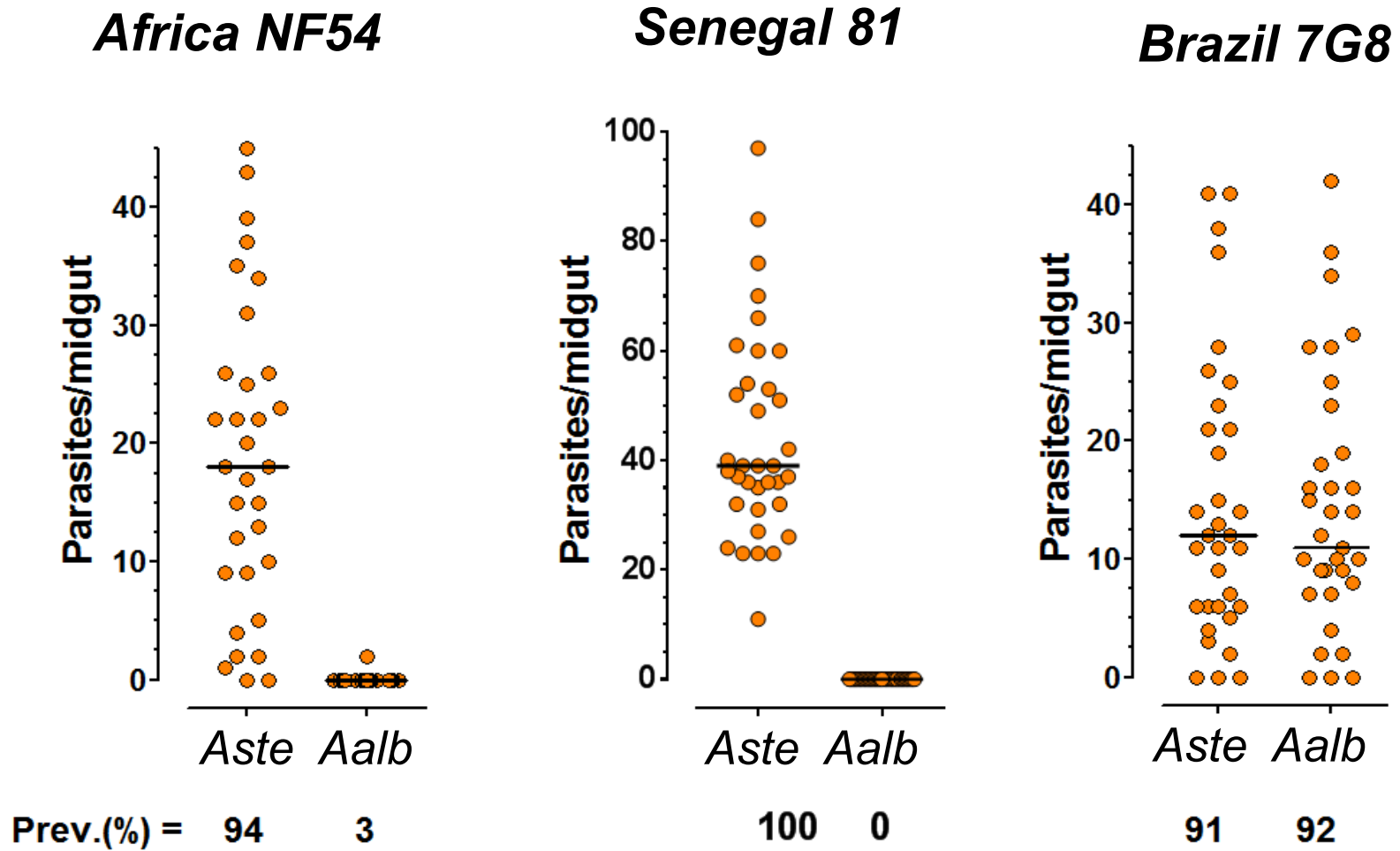
Geographic distribution of *Anopheles* spp.



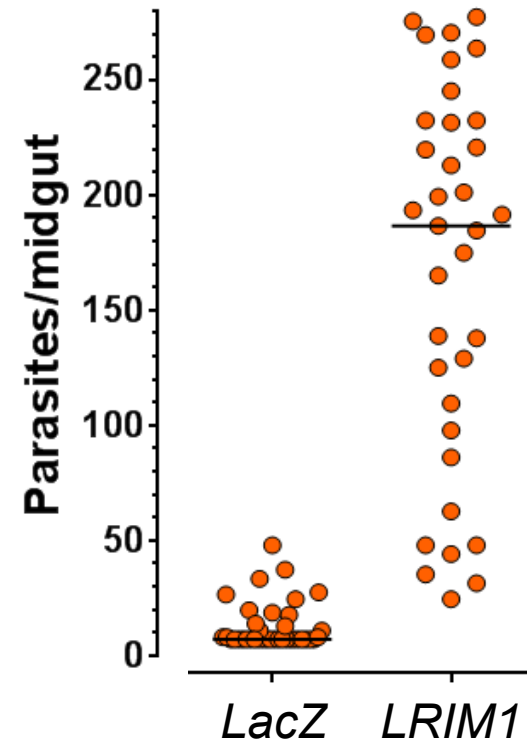
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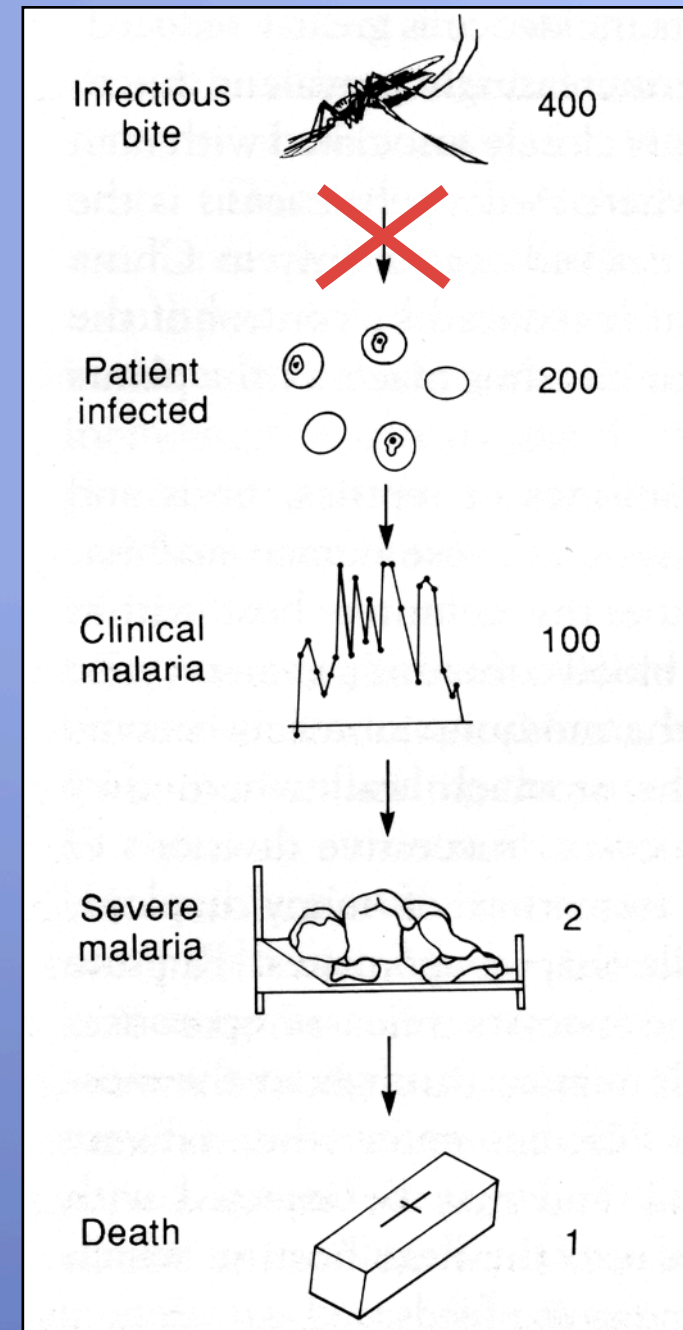
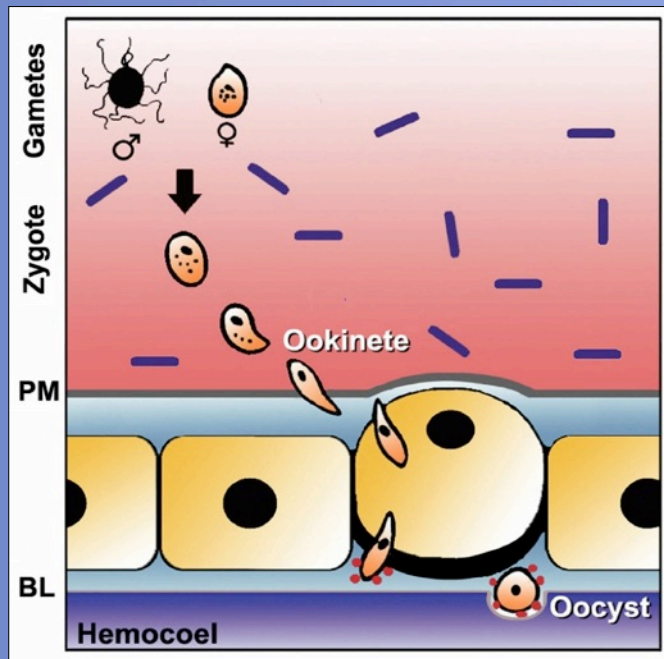


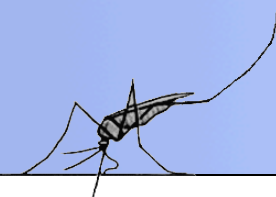
Anopheles albimanus



Africa NF54


$$\text{Prev.(\%)} = \frac{42}{100}$$





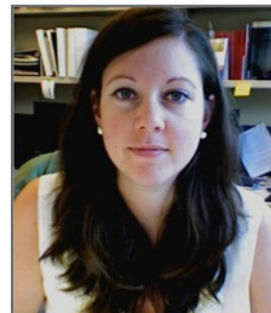
Mosquito Immunity and Vector Competence Unit



Giselle De Almeida



Joshua Lieberman



Lindsey Garver



Alvaro Molina-Cruz



Ashley Haile



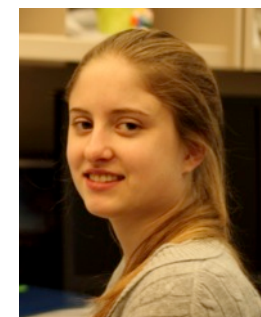
Corrie Ortega



Jared Winikor



Amy Alabaster



Lois Bangiolo

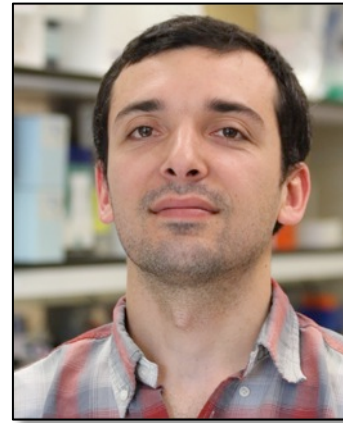
Mosquito Immunity and Vector Competence Unit



Jose Luis Ramirez



Urvashi Ramphul



Gaspar Canepa



Julio Castillo



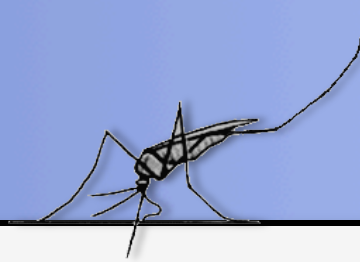
Emma Taylor-Salmon



Rebecca Greene



Nitin Kamath



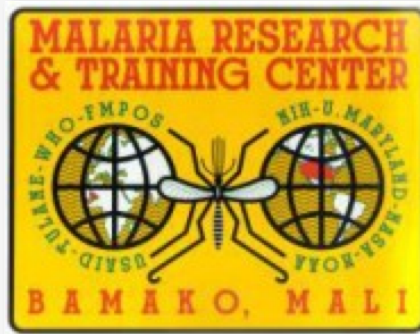
Future Plans



Oliver Billker
Sanger Institute



Martin Boulanger
University of Victoria



Nafomon Sogoba
Cheick Traore
*MRTC, Bamako,
Mali*



Isabelle Morlais
*OCEAC, Yaoundé,
Cameroon*



Paulo Pimenta
*Inst. Rene Rachou, Fiocruz
Belo Horizonte, Brazil*

Laboratory of Malaria and Vector Research National Institutes of Health.

